Treatment with the SQ-Standardised Grass Allergy Immunotherapy Tablet is well Tolerated in Children, Adolescents and Adults in Real Life Application—A Non-Interventional Observational Study

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Abstract

Background: Efficacy and safety of the SQ-standardised grass allergy immunotherapy tablet (GRAZAX®) has been reported in a large number of randomised, controlled clinical trials in children and adults performed in Europe and the US. GRAZAX® became available for routine treatment in children from 5 years of age in Germany and Austria in 2008. To examine the safety and tolerability of GRAZAX® in patients that were less highly selected as in the controlled trials we performed an open label, uncontrolled, non-interventional study in children and adults who were routinely treated in allergists’ offices.

Materials and methods: Patients with allergic rhinoconjunctivitis with or without asthma were treated with GRAZAX® and observed for 3-4 visits every 3 months with the last visit after the first grass pollen season. Adverse drug reactions were documented at first administration and at the subsequent visits, and patients were requested to rate their satisfaction with treatment and their symptoms and symptomatic medication requirements for grass pollen seasons before and during therapy.

Results: Treatment was documented in 1,761 patients (797 <18 years; 964 ≥18 years) treated by 373 allergists in Germany and Austria between November 2008 and January 2010. Adverse drug reactions were reported in 31.8% of patients (27.3% ≥18 years, 37.3% <18 years). The higher number of patients <18 years with reactions was due to a higher frequency of local oral reactions. The overall tolerability profile was similar in children and adults. Nasal symptoms improved in 82.7% of patients and no or less symptomatic medication was used by 89.7%. The compliance was rated >75% in 89.8% of patients, >95% of patients and physicians were satisfied with treatment.

Conclusion: The results of our study confirm the safety and tolerability profile observed in controlled clinical trials with GRAZAX®. Treatment satisfaction during routine application was rated high and was combined with a high compliance.

Keywords: Allergy immunotherapy tablet; GRAZAX®, Phleum pratense; Rhinoconjunctivitis; Sublingual immunotherapy; Tolerability

Abbreviations: ADR: Adverse Drug Reaction; AIT: Allergy Immunotherapy Tablet; GPS: Grass Pollen Season; SADR: Serious Adverse Drug Reaction; SIT: Specific Immunotherapy; SQ: Standardised Quality; V: Visit

Introduction

Allergic rhinoconjunctivitis represents a global health problem affecting 10-25% of the population and the number appears to be rising [1,2]. The condition is one of the main reasons for visits to primary care clinics and although usually not regarded as a severe disease it may significantly limit the quality of life of the patient as well as affecting school learning performance and work productivity [1].

Today, the treatment of allergic diseases is based on allergen avoidance, pharmacotherapy for symptom relief, and allergen-specific immunotherapy, the latter being the only treatment modality proven to alter the natural course of the disease, thereby entailing sustained reductions in symptoms [3]. Subcutaneous allergen injections have been the main approach for the administration of immunotherapy, however, this has subsequently been extended to sublingual administration, which offers several advantages compared with the subcutaneous route, including increased convenience and compliance [4-7].

The SQ-standardised grass allergy immunotherapy tablet (AIT, GRAZAX®), developed for sublingual application in patients with grass pollen induced rhinoconjunctivitis was first launched in November 2006 in Germany after gaining marketing authorisation in several European countries. Marketing authorisation was extended to include treatment of children from 5 years of age in November 2008.

The clinical efficacy and favourable tolerability profile of grass AIT has been reported in a large number of randomised, controlled trials in adults and children performed in Europe and the US [8-22]. The most common adverse events (AEs) associated with grass AIT have been mild to moderate local reactions in the mouth or throat (e.g. oral pruritus) occurring most frequently after first administration and during the initial treatment phase [8-15]. Therapy with grass AIT is recommended...
to be continued for a period of 3 years. Safety and tolerability in a real-life setting have been investigated in adults in a phase IV clinical trial for three consecutive grass pollen seasons in France [23].

The objective of our present non-interventional, observational and open-label study was to investigate safety and tolerability of grass AIT in children, adolescents and adults during routine treatment by practising allergists in a real life setting. In addition, data for compliance, treatment satisfaction and treatment effect of grass AIT were recorded.

Materials and Methods

Study design

The study was designed as a multi-centre, open, uncontrolled and observational study for the period of start of grass AIT (GRAZAX®, Phleum pratense 75,000 SQ-T/2,800 BAU, ALK, Hørsholm, Denmark) until the end of the first grass pollen season. Study visits were performed at start of therapy and then 3 to 4 visits every 3 months when the patient came into the physician’s office for a new prescription.

The centers participating in this study were distributed evenly across Germany and Austria. For this purpose allergists applying specific immunotherapy were registered in regional lists and were asked for participation in the study in a randomly arranged new order. The centres were asked to record data for 5 to 10 patients in a consecutive order dependent on the patients’ willingness to participate in the study. Together, the random selection of centres and the consecutive choice of study patients represent a suitable measure to avoid a selection bias in the study population. Physicians were asked to document all patients who were potentially eligible for the study in a patient’s log; thus, the selection process remained fully transparent.

The study included patients who started their treatment by specific immunotherapy with grass AIT from November 2008. Patients were observed until the end of the first grass pollen season with grass AIT during their intended treatment period of 3 years.

The study was conducted in 373 allergy's centers (360 in Germany and 13 in Austria) between November 2008 and January 2010 and included 1,761 patients (1,718 in Germany and 43 in Austria) suffering from rhinoconjunctivitis to grass pollen with or without asthma. All patients with rhinoconjunctivitis symptoms and indication for specific immunotherapy for whom the decision to apply grass AIT (GRAZAX®) had been taken independently of the study were eligible for documentation in the study.

Assessments

The time schedule and the major observations of the study are illustrated in Figure 1. At visit 1 (V1) when the patient was included in the study demographic data and data on the allergy history including age at first appearance of symptoms, clinical manifestation of the allergy (rhinitis/conjunctivitis/asthma/atopic dermatitis), other allergies, the diagnostics performed and previous specific immunotherapy (SIT) treatment, if applicable, were recorded. The symptoms and medication use in the previous grass pollen season (GPS) were recorded retrospectively as nasal, ocular, bronchial and skin symptoms assessed on a scale 0 to 3 (no/mild/moderate/severe) and the different types of symptomatic medication that had been used (topical nasal and eye drops/oral antihistamines/oral corticosteroids/bronchial β-sympathomimetics/bronchial corticosteroids/other, to be specified) were recorded. Patients were asked about their satisfaction with the symptomatic medication in the previous GPS (very satisfied/satisfied/dissatisfied/very dissatisfied), and concomitant treatments, SIT or other medication due to concomitant diseases were recorded. At V1 the first administration of grass AIT was performed and adverse drug reactions (ADRs) were recorded that occurred while the patient remained under observation for a period of 30 minutes in the clinic.

ADRs were specified by the physician in the case report form (CRF) as diagnosis or description and assessed by intensity (mild/moderate/severe), causality (no relation/relation unlikely/possible/probable/certain/unknown), treatment by medication (yes/no) and medical treatment applied, outcome (recovered/recovering/recovered with sequelae/not recovered/fatal/unknown) and seriousness (yes/no). ADRs were assessed as severe when the events considerably interfered with the patient’s daily activities. A serious ADR (SADR) 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 defect, or any other event judged medically important.

Subsequently, the patients came to the clinic every 3 months for a new prescription (100 tablets of grass AIT). At visit 2 (V2) and visit 3 (V3) information given by the patient on ADRs of grass AIT were recorded by the physician. The compliance rate of the patient was estimated by the physician (>95%/>75% to 95%/≥ 50% to 75%/<50%) with ratings >75% considered as compliance. Furthermore, it was assessed whether the patient found the administration of the grass AIT easy or difficult and the convenience of administration was assessed (convenient/acceptable/inconvenient). At visit 4 (V4) the same assessments as at V2 and V3 were performed and, in addition, symptoms and medication in the first GPS with grass AIT recorded according to parameters exercised at V1. The well-being of the patient with grass AIT compared to previous years (much better/better/unchanged/worse/much worse) was also assessed and patients and physicians rated their satisfaction with grass AIT (very satisfied/satisfied/dissatisfied/very dissatisfied). The patient was further asked to what extent the ADRs affected his/her physical well-being and mental ability and his/her global satisfaction with grass AIT (no impact at any time/impact over a short period/impact over a considerable period/impact all of the time). Finally, it was recorded whether the patient continued treatment beyond the end of the observation period or discontinued and the reasons in case of discontinuation. If V3 was performed post-seasonal, V4 was omitted.
21.6% of patients on day 1 of treatment. During the entire treatment (± 2.6 SD) and for 1,512 patients follow-up information after the end of the study. The average duration of treatment was 6.4 months physician. In total, 1,150 (65.3%) patients continued treatment after the 7.4% of patients no further information was provided by the treating physician. In total and for 1,381 (78.4%) patients for a seasonal disease.

Safety and tolerability

Data on safety and tolerability are displayed in Table 3. ADRs after the first administration of grass AIT were reported in 18.9% of patients within 30 minutes under supervision of the physician and in 21.6% of patients on day 1 of treatment. During the entire treatment period ADRs were reported in 31.8% of patients. The frequency of ADRs was generally higher in patients <18 years than in adult patients (37.3% of patients <18 years vs. 27.3% of adult patients). Most of the reactions were of mild or moderate intensity in all patients; 6.7% of the patients reported ADRs classified as severe. In patients <18years the proportion of patients with mild ADRs was higher than in the adult group (18.7% vs.11.8%). In 8.6% of patients the ADRs were treated by medication and in 8.1% of patients the treatment was terminated due to ADRs. ADRs classified as serious were reported in 6 patients (0.3%), in 1 patient <18 years and in 5 adult patients. In an 11-years-old boy dyspnoea, chest pain and abdominal pain was reported at day 17 of treatment with symptoms for 1.5 hours that were treated with inhaled epiinephrine, corticosteroids and antihistamine and classified as medically important; the patient discontinued treatment. In a 31-years-old female patient swollen lips and tongue and asthma were reported and treated with inhaled epiinephrine, corticosteroids and antihistamine, and in an 18-years-old female patient paraesthesia lips, throat swelling, cough and asthmatic attack, both at day 1 of treatment and treated with systemic corticosteroid, antihistamines and beta-sympathomimetics; the patients discontinued treatment. In a 47-years-old female patient

| Patients ≤18 years N (%) | Patients ≥ 18 years N (%) | Total patients N (%) |
|-------------------------|----------------------------|----------------------|
| First intake of grass AIT | 797                        | 964                  | 1,761                |
| Follow-up information available | 711 (89.2) | 801 (83.1) | 1,512 (85.9) |
| At least 1 Follow-up visit | 693 (87.0) | 784 (81.3) | 1,477 (83.9) |
| Seasonal or post-seasonal visit | 652 (81.8) | 729 (75.6) | 1,381 (78.4) |
| Premature study termination due to Adverse events | 72 (9.0) | 71 (7.4) | 143 (8.1) |
| Contraindication, intercurrent disease | 4 (0.5) | 2 (0.2) | 6 (0.3) |
| Pregnancy, wish to have a child | - | 8 (0.8) | 8 (0.5) |
| Wish of patient/patients; patient refused administration | 19 (2.4) | 8 (0.8) | 27 (1.5) |
| Change-over to another drug | 8 (1.0) | 13 (1.3) | 21 (1.2) |
| Other reasons | 7 (0.9) | 21 (2.2) | 28 (1.6) |
| Lacking compliance | 76 (9.5) | 171 (17.7) | 247 (14.0) |
| Unknown (no information available) | 45 (5.6) | 86 (8.9) | 131 (7.4) |
| Treatment continued after end of study | 566 (71.9) | 584 (60.6) | 1,150 (65.3) |

Table 2: Flow of patients through the study for pediatric patients (<18 years), adults (≥ 18 years) and total patients treated with the grass allergy immunotherapy tablet (AIT).
an asthmatic attack and breathing difficulties were reported at day 2 of treatment and treated with antihistamines and cromoglicate, the patient continued treatment; in a 42-years-old male an asthmatic attack was reported at day 35, the patient discontinued treatment; ADRs were classified as medically important for these patients. In a 71-years-old female patient swollen lips and tongue were reported at day 33 of treatment and treated with corticosteroids and antihistamines. The patient was hospitalised overnight for observation and discontinued treatment.

Oral paraesthesia, throat irritation, oral pruritus and mouth oedema were mostly frequently observed as ADRs. ADRs most frequently reported (≥ 1% of patients) are shown in Figure 2. Oral reactions were observed with higher frequencies in patients <18 years compared to the adult patient group resulting in the higher frequency of ADRs in patients <18 years for the entire treatment period. ADRs were assessed to have an impact on the physical well-being and mental ability in 10.9% of patients <18 years and in 14.2% of adult patients ‘over a considerable period’ or ‘all of the time’, and to have an impact on global satisfaction with grass AIT in 15.3% of patients <18 years and 17.6% of adult patients.

Compliance, treatment satisfaction and effect of treatment

Compliance was rated >75% in 1,326 (89.8%) patients without differences between the age groups. The treatment with grass AIT was discontinued due to non-compliance in 76 (9.5%) patients <18 years and in 171 (17.7%) adult patients. In 131 (7.4%) patients no further information was provided by the physician. The administration of grass AIT as prescribed was assessed as ‘easy’ in 94.7% of patients <18 years and 97.4% of adult patients; 97.0% assessed the convenience of the application of grass AIT as ‘convenient’ or ‘acceptable’ (3.0% as ‘inconvenient’).

Patients who improved in the first GPS with grass AIT compared with the previous season before grass AIT were considered as responders to treatment. Responders were 82.7% of patients for nasal symptoms, 80.4% for eye symptoms, 77.9% for bronchial symptoms and 76.2% for skin symptoms. Response rates were observed to be higher for patients <18 years than for adult patients (nasal symptoms 84.0% vs. 81.5%, eye symptoms 85.0% vs. 76.4%, bronchial symptoms 83.5% vs. 72.6%, skin symptoms 79.2% vs. 73.0%). The use of symptomatic medication decreased for all patients from 79.1% of patients in the previous GPS to 46.9% patients in the season with grass AIT; 45.2% of patients who used medication in the previous GPS before grass AIT did not take any medication in the GPS with grass AIT and 44.5% of patients used less medication. No symptomatic medication or less medication was used in the season with grass AIT by 92.6% of patients <18 years and 86.9% of patients ≥ 18 years who had used symptomatic medication in the season before grass AIT. The well-being of the patients during grass AIT as compared with the previous GPS was assessed by 90.4% of patients to be ‘better’ or ‘much better’ (93.2% <18 years, 87.8% adults); 95.9% of patients (97.5% <18 years, 94.4% adults) were ‘very satisfied’ or ‘satisfied’ with grass AIT; physicians were ‘very satisfied’ or ‘satisfied’ with grass AIT in 96.4% of patients (96.7% of patients <18 years, 96.1% of adults).

Discussion

In this large non-interventional observational study on routine application of grass AIT data on safety and tolerability were recorded in 1,761 patients with moderate to severe rhinoconjunctivitis (797 patients aged between 4 and 17 years and 964 adult patients) who were routinely treated in Germany and Austria between November 2008 and January 2010. The study was initiated after grass AIT had become available for children from 5 years of age in Germany and Austria in 2008. Data about safety and tolerability are presented for large patient groups <18 years of age and ≥ 18 years treated in a real-life setting and outside of controlled clinical trials where patients are highly selected.

Out of 1,761 patients who first applied grass AIT 1,150 patients (65.3%) continued treatment after the end of the observation period. Reasons for discontinuation of treatment were lacking compliance (14% of patients), ADRs (8.1%) and contraindications, intercurrent disease, pregnancy or wish to have a child, or refusal to continue administration of grass AIT, change to another drug or other reasons (5.1%). Continuation of treatment was unknown in 7.4% of patients because the physicians did not provide further information. The rate of discontinuation in our study was higher than in the phase IV clinical trial investigating safety and tolerability in a real-life setting in adults in France in which 83.3% of patients who had started grass AIT pre-seasonally were still in the trial at the end of the first grass pollen season and 75.1% at the end of the first year [21].

Grass AIT was generally well tolerated. ADRs during first administration in the clinic were reported in 18.9% of all patients treated with a slightly higher proportion of patients in the group <18 years of age (20.7%). For the entire treatment period the rate of ADRs reported in the patient group <18 years of age was 37.3% and 27.3% in the adult patient group. The higher frequency in the patient group <18 years may be explained by the fact that the two groups of patients had not the same severity of the allergic disease. Patients <18 years had more severe rhinoconjunctivitis symptoms (primarily more severe eye symptoms), they used more symptomatic medication in the previous GPS and more patients in the group <18 years had asthma. The higher rate of reactions in the patient group <18 years was due to a higher frequency of well-known ADRs of mild intensity (18.7% of patients <18 years with mild reactions and 10.4% in the adult group). These ADRs were primarily located at the application site in the mouth and included reactions such as oral paraesthesia, throat irritation, oral pruritus and mouth oedema. This pattern of reactions corresponds to the known safety profile from controlled clinical trials in children and adults as described in the SmPC and is in agreement with data from other previous non-interventional studies in adults [8-20].

Grass AIT was assessed to be applied with high compliance. About 90% of patients independently of age were assessed to have a compliance rate >75%. Treatment was more frequently discontinued...
due to compliance reasons in the adult patient group than in the group of patients <18 years of age. The application of grass AIT was assessed to be easy and convenient in >95% of subjects. Changes in symptoms and medication use in the GPS with grass AIT compared with the previous GPS before grass AIT were evaluated as effectiveness of therapy. Nasal and eye symptoms improved in approximately 80% of patients with higher rates in patients <18 years of age than in the adult patient group and about 90% of total patients who used no or less medication in the GPS with grass AIT. This was in agreement with 90% of patients who assessed their well-being in the GPS as improved compared with the previous GPS and a high satisfaction rate with treatment by patients and physicians in >95% of patients.

In conclusion, grass AIT treatment was well tolerated in this non-interventional observational study in children, adolescents and adults. The safety profile is in agreement with data from controlled clinical trials in adults and children. Compliance, satisfaction with treatment and effectiveness were assessed to be high.

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Conflicts of Interests

C Gronke received remuneration from ALK for the documentation of patient data from her clinic for this study and honoraria from ALK for oral presentations. J Schnitker was funded by ALK as CRO in the study. H Wolf and E Wüstenberg are employees of ALK. Previous presentations as abstracts or posters:

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References

1. Bousquet J, Van Cauwenberge P, Haltaev N; Aria Workshop Group; World Health Organization (2001) Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 108: S147-S334.
2. Linneberg A, Gislum M, Johansen N, Husemøn LL, Jørgensen T (2007) Temporal trends of aeroallergen sensitization over twenty-five years. Clin Exp Allergy 37: 1137-1142.
3. EMEA (2008) Guideline on the clinical development on products for specific immunotherapy for the treatment of allergic diseases. Report No.: CHMP/EWP/185504/2006.
4. Senel S, Kremer M, Nagy K, Squier C (2001) Delivery of bioactive peptides and proteins across oral (buccal) mucosa. Curr Pharm Biotechnol 2: 175-186.
5. Bagnasco M, Morbelli S, Altrinetti V, Falagiani P, Mariani G, et al. (2003) Allergen biodistribution in humans. Chem Immunol Allergy 82: 33-43.
6. Bagnasco M, Altrinetti V, Pesce G, Caputo M, Mistrello G, et al. (2005) Pharmacokinetics of Der p 2 allergen and derived monomeric allergoid in allergic volunteers. Int Arch Allergy Immunol 138: 197-202.
7. Moingeon P, Batard T, Fadel R, Frati F, Sieber J, et al. (2006) Immune mechanisms of allergen-specific sublingual immunotherapy. Allergy 61: 151-165.
8. Malling HJ, Lund L, Ipsen H, Poulsen L (2006) Safety and immunological changes during sublingual immunotherapy with standardized quality grass allergen tablets. J Invest Allergol Clin Immunol 16: 162-168.
9. Kleine-Tebbe J, Rübel M, Herold DA (2006) Safety of a SQ-standardised grass allergen tablet for sublingual immunotherapy: a randomized, placebo-controlled trial. Allergy 61: 181-184.
10. Calderón M, Essendrop M (2006) Specific immunotherapy with high dose SQ standardized grass allergen tablets was safe and well tolerated. J Invest Allergol Clin Immunol 16: 338-344.
11. ibañez MD, Kaiser F, Knecht R, Armentia A, Schöpfer H, et al. (2007) Safety of specific sublingual immunotherapy with SQ standardized grass allergen tablets in children. Pediatr Allerg Immunol 18: 516-522.
12. Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S (2006) Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 117: 802-809.
13. Dahl R, Kapp A, Colombo G, de Monchy JG, Rak S, et al. (2006) Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 118: 434-440.
14. Dahl R, Stender A, Rak S (2006) Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. Allergy 61: 185-190.
15. Bufo A, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, et al. (2009) Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. J Allergy Clin Immunol 123: 167-173.
16. Dahl R, Kapp A, Colombo G, de Monchy JG, Rak S, et al. (2008) Sublingual grass allergen tablet immunotherapy provides sustained clinical benefit with progressive immunologic changes over 2 years. J Allergy Clin Immunol 121: 512-518.
17. Durham SR, Emminger W, Kapp A, Colombo G, de Monchy JG, et al. (2010) Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. J Allergy Clin Immunol 125: 131-138.
18. Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S et al. (2012) SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. J Allergy Clin Immunol 129: 717-725.
19. GRAZAX® (75,000 SQ-T oral lyliphsilate) [summary of product characteristics] (2009) Wedel, Germany: ALK.
20. Calderon MA, Birk AO, Andersen JS, Durham SR (2007) Prolonged preseasonal treatment phase with Grazax sublingual immunotherapy increases clinical efficacy. Allergy 62: 958-961.
21. Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, et al. (2011) Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. J Allergy Clin Immunol 127: 64-71, 71.
22. Nelson HS, Nolte H, Creticos P, Maloney J, Wu J, et al. (2011) Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. J Allergy Clin Immunol 127: 72-80, 80.
23. Wessel F, Chartier A, Meunier JP, Magnan A (2012) Safety and tolerability of an SQ-standardized GRAss ALergy immunotherapy tablet (GRAZAX®) in a real-life setting for three consecutive seasons-the GRAAL trial. Clin Drug Investig 32: 451-463.