Safety and Tolerability of an Intra-seasonal Initiation of the SQ-Standardised Grass Allergy Immunotherapy Tablet: A Non-interventional Observational Study Investigating the Feasibility During Routine Administration

Jan-Alexander Schwab · Hendrik Wolf · Jörg Schnitker · Eike Wüstenberg

Published online: 13 August 2013 © The Author(s) 2013. This article is published with open access at Springerlink.com

Abstract
Background and Objective For specific immunotherapy to pollen allergy, a pre-seasonal start of treatment is recommended by international guidelines. In a placebo-controlled clinical trial with adults, an intra-seasonal start of therapy with the SQ-standardised grass allergy immunotherapy tablet (AIT) was well-tolerated. The objective of our study was to investigate the feasibility of an intra-seasonal start of grass AIT administered during routine treatment by practising allergists.

Methods In a multicentre, prospective, open-label, uncontrolled, non-interventional observational study, data on routine treatment with grass AIT were recorded in patients who started administration of tablets within the 2010 grass pollen season in Germany. Adverse events (AEs) were recorded by the physician at visits for the first administration in the clinic and at the end of the 1- to 3-month observation period. AEs and daily administration of the tablet were recorded by the patients in diaries for the first 14 days. Treatment satisfaction, global tolerability and perceived effect of treatment were assessed by the patient and physician at the end of the study.

Results A total of 662 patients were treated with 1 tablet daily by 286 physicians. Grass AIT was started intra-seasonally in 620 patients and post-season in 42. The average treatment period was 51.6 days. AEs were recorded in 52.1 % of all patients and in 35.6 % at first administration, with throat irritation (21.3 %), paraesthesia oral (19.9 %), oral pruritus (14.0 %) and ear pruritus (10.3 %) being the most frequent AEs related to grass AIT. The intensity of the AEs was assessed as mild or moderate in 42.1 % of patients and severe in 8.0 %; AEs related to grass AIT were classified as serious in two patients. Grass AIT was discontinued due to AEs in 7.7 % of patients. Diaries were evaluable for 77.0 % of patients; the average rate of patients with AEs decreased continuously from 44.7 % (day 1) to 26.9 % (day 14) and the average daily rate of patients who forgot to take their tablet was about 5 %. Overall tolerability was assessed by 87.2 % of patients and 91.4 % physicians as “very good” or “good” and effectiveness of treatment was assessed as “very good” or “good” in 81.4 % of patients and 85.8 % of physicians. More than 90 % of patients and physicians were satisfied with the treatment.

Conclusion The tolerability data for an intra-seasonal start of grass AIT during routine treatment confirm the safety profile from the previous controlled trial. Tolerability was assessed as good in combination with high satisfaction with the treatment and compliance.

1 Introduction

Allergic rhinoconjunctivitis represents a global health problem, affecting approximately one-quarter of the
European population [1, 2]. Specific immunotherapy (SIT) is the only treatment modality with the potential to alter the natural course of the disease and offer sustained reductions in symptoms after treatment discontinuation [3].

The first immunotherapies were administered subcutaneously by physicians (allergen injections), but today’s treatments have been extended to sublingual administration by daily drop-based formulations as well as to an allergy immunotherapy tablet (AIT). Sublingual administration offers several potential advantages compared with the subcutaneous route, including increased convenience and an improved tolerability profile [overcoming concerns regarding systemic adverse events (AEs) associated with subcutaneous administration] [1, 4, 5].

Grass AIT has been approved for marketing in several European countries for the disease-modifying treatment of grass pollen-induced rhinoconjunctivitis in adults and children (5 years or older). The clinical efficacy and favourable tolerability profile of grass AIT has been reported in a series of randomised controlled trials in adults and children [6–15]. Furthermore, sustained clinical efficacy and disease modification 2 years after completion of 3 years of treatment with grass AIT has recently been demonstrated in a double-blind, multinational, placebo-controlled trial [16]. The most common AEs associated with grass AIT have been mild to moderate local reactions in the mouth or throat (e.g. oral pruritus), predominantly occurring after first administration or during the initial treatment phase [6–13].

For initiation of SIT, patients are usually asked to return after the grass pollen season when they are no longer exposed to grass pollen. The possibility of intra-seasonal treatment initiation may be of interest to patients and prescribing physicians because allergy patients often first contact the physician due to symptoms during the grass pollen season. However, because patients may be less motivated to initiate immunotherapy when symptoms decline after the grass pollen season, treatment may not be started in a considerable proportion of these patients. As a result, many of these patients are likely to present again in the following season with sub-optimally controlled symptoms.

In a multicentre, randomised, double-blind, placebo-controlled phase III trial, intra-seasonal initiation of grass AIT was associated with an immunomodulatory response in terms of induction of immunoglobulin (Ig) E-blocking factor, specific IgE and specific IgG4. Furthermore, the intra-seasonal-initiated therapy was generally well-tolerated [17].

Systematically recorded data on safety and tolerability of the intra-seasonal start of grass AIT in real life are needed to evaluate the benefit and risks in daily use.

The objective of our non-interventional, observational study was, therefore, to investigate the feasibility of an intra-seasonal start of grass AIT during routine administration under real life conditions.

2 Methods

2.1 Study Design and Treatment

In this non-interventional, open-label, uncontrolled observational study the treatment of patients who started grass-AIT administration within the summer grass pollen season between June and August 2010 in Germany was planned to be documented by 286 allergologically trained physicians distributed across Germany.

For treatment with grass AIT GRAZAX® (Phleum pratense 75,000 SQ-T/2,800 BAU, ALK, Hørsholm, Denmark) was applied.

Centres were asked to participate in the study according to regional random lists of allergists applying SIT and were asked to record data on two to three patients in consecutive order, dependent on the patient’s willingness to participate in the study, in order to avoid a selection bias. Physicians were asked to document all patients who were potentially eligible to be included in a patient log.

2.2 Participants

Data on patients with a diagnosis of grass pollen-induced rhinitis and/or conjunctivitis (according to symptoms, skin prick test or RAST) with or without asthma with clinically relevant symptoms who had no contraindications to a prescription of grass AIT according to the Summary of Product Characteristics for GRAZAX® [18] were eligible to be documented in this study. Contraindications included hypersensitivity to any of the excipients of the AIT, malignancy or systemic diseases affecting the immune system, e.g. autoimmune diseases, immune complex diseases or immune deficiency diseases; inflammatory conditions in the oral cavity with severe symptoms such as oral lichen planus with ulcerations or severe oral mycosis; and patients with uncontrolled or severe asthma (forced expiratory volume in 1 second <70 % of predicted value after adequate pharmacological treatment in adults and <80 % in children). The study plan was approved by the Ethics Committee of the Landesärztekammer Baden-Württemberg and patient consent for the collection of their data was obtained.

2.3 Data Collection

The time schedule and the major observations of the study are illustrated in Fig. 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,
any previous treatment by SIT, and concomitant treatments by SIT or other medications due to concomitant diseases were recorded. Symptoms and medication use in the previous grass pollen season were recorded retrospectively. Symptoms were recorded as nasal, ocular, bronchial and skin symptoms assessed on a scale from 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) were recorded. The first administration of the grass AIT was performed in the clinic, where an eventual anti-allergic premedication was recorded as well as any AEs that occurred while the patient was under observation for 30 min. An AE was defined as any untoward medical occurrence in a patient who was administered grass AIT and which did not necessarily have a causal relationship with treatment. AEs that were possibly related to treatment were classified as adverse drug reactions (ADRs). For the first 2 weeks of therapy, patients were asked to enter the administration of the grass AIT and all AEs and the respective actions they had taken (medication taken/physician contacted) in a diary. AEs were specified by the physician in the case report form (CRF) as diagnosis or description and assessed by intensity (mild/moderate/severe), causality (possible/unlikely), change of treatment (no change/interruption/discontinuation), treatment by medication (yes/no), outcome (recovered/improved/recovered with sequelae/not recovered/fatal/unknown) and whether it was serious (yes/no). An AE was assessed as severe when the event considerably interfered with the patient’s daily activities. A serious AE (SAE) 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.

The patients came back to the clinic after 1–3 months [visit 2 (V2)] for a new prescription, depending on whether 30 or 100 tablets of grass AIT had been prescribed. At V2 the physician interviewed the patients about AEs that occurred between V1 and V2 during home treatment and recorded all AEs in the CRF, including his assessment. Furthermore, the overall compliance of the patient during the observation period was assessed by the physician according to overall compliance rates of <50, 50 to <80 or ≥80 %: with a rate of ≥80 % the patient was considered to be compliant with grass AIT. Symptoms and medication after 1–3 months of treatment with grass AIT were recorded and compared with data obtained at V1 and the well-being of the patient with grass AIT compared with previous years (much better/better/unchanged/worse/much worse) was assessed. Patients and physicians rated their satisfaction with grass AIT (very satisfied/satisfied/unsatisfied/very unsatisfied) and globally assessed the tolerability (very good/good/moderate/poor) and overall effectiveness of therapy (very good/good/moderate/no effect/not assessable). Finally, the continuation or discontinuation of treatment and its reasons were recorded.

2.4 Statistical Methods

In order to investigate tolerability, the aim was to include at least 600 patients to be able to detect an ADR with an incidence of 1 % with a 99 % probability at least once. Therefore, the aim was to include about 300 physicians distributed all over Germany in our study, each recording data from two to three patients. Statistical analyses were performed using SAS software, versions 8.2, 9.1.3 and 9.2 (SAS Institute, Cary, NC, USA). The statistical analysis was performed by descriptive statistical methods using mean, median, standard deviation and range. Test procedures were not used. In the all-patients-treated set of the study the patients were classified as “intra-seasonal” (June–August 2010) and “post-seasonal” (September 2010 or later) with respect to their start of treatment and the respective data presented separately. Reasons for premature termination were non-compliance, AEs, medical
reasons, insufficient effectiveness, improvement or other reason. AEs were coded according to the current version of the Medical Dictionary for Regulatory Activities (MedDRA). AEs and ADRs were displayed for patients and events. All parameters that had been documented for the study were evaluated for the number of patients who had respective entries in the CRFs. Missing data were not replaced.

3 Results

3.1 Patients

Data for 662 patients from 286 sites who had their first intake of grass AIT in the clinic and had been treated for 51.6 days on average could be evaluated. In a small proportion of these patients treatment had been started after the end of the grass pollen season (later than August). Therefore, patients were stratified according to the start of treatment into the following subgroups: intra-seasonal start of treatment (until 31 August 2010, \( n = 620; 93.7 \% \)) and post-seasonal start of treatment (after 31 August 2010, \( n = 42; 6.3 \% \)). The patients’ demographic data at start of grass AIT (V1) are summarised in Table 1.

After the first administration in the clinic, 53 patients did not return for the follow-up visit, but 18 patients sent their diary to the physician by mail, so 627 patients in total could be evaluated with respect to the tolerability of the second and further administrations of grass AIT. Diaries were evaluable for 510 (77.0 \%) patients. The flow of patients through the study is shown in Fig. 2.

3.2 Safety and Tolerability

During the entire observation period AEs were observed in 345 (52.1 \%) of the 662 total patients, and in 320 (51.6 \%) of 620 patients who started grass AIT intra-seasonally and 25 (59.5 \%) of 42 patients who started grass AIT post-season. Data on AEs observed during the study are displayed in Table 2.

During first administration of grass AIT, AEs were recorded in 236 (35.6 \%) of the total patients, and in 215 (34.7 \%) patients who started grass AIT intra-seasonally and in 21 (50.0 \%) patients who started grass AIT post-season.

Most AEs were assessed as possibly related to grass AIT and were, therefore, ADRs. The majority of the reactions were of mild or moderate intensity. Severe reactions were recorded in 48 (7.7 \%) patients with intra-seasonal start of grass AIT and in 5 (11.9 \%) patients with post-seasonal start; 10.9 \% of patients were treated with medication due to AEs and 7.7 \% discontinued treatment with grass AIT due to AEs.

Table 1 Patient characteristics

| Parameter | Start of treatment | Total |
|-----------|-------------------|-------|
|           | Intra-seasonal \( (n = 620) \) | Post-seasonal \( (n = 42) \) | \( (n = 662) \) |
| Median age (years) | 29.0 | 28.5 | 29.0 |
| Range (years) | 5–78 | 12–64 | 5–78 |
| Patients <18 years [\( n \ (% \)] | 72 (11.6) | 3 (7.1) | 75 (11.3) |
| Sex [\( n \ (% \)] | | | |
| Male | 297 (47.9) | 18 (42.9) | 315 (47.6) |
| Female | 323 (52.1) | 24 (57.1) | 347 (52.4) |
| BMI (kg/m\(^2\)) [mean ± SD] | 24.2 ± 4.6 | 23.9 ± 3.4 | 24.2 ± 4.6 |
| Symptoms [\( n \ (% \)] | | | |
| Moderate-to-severe nasal symptoms | 564 (91.0) | 38 (90.5) | 602 (91.0) |
| Moderate-to-severe eye symptoms | 437 (70.4) | 31 (73.8) | 468 (70.7) |
| Asthma | 148 (23.9) | 15 (35.7) | 163 (24.6) |
| Allergy history | | | |
| Mean duration (±SD) since diagnosis of grass pollen allergy (years) | 6.0 ± 8.8 | 7.1 ± 8.8 | 6.1 ± 8.8 |
| History of immunotherapy [\( n \ (% \)] | 153 (24.7) | 19 (45.2) | 172 (26.0) |
| Symptomatic medication taken during last season [\( n \ (% \)] | | | |
| No | 126 (20.4) | 10 (24.4) | 136 (20.6) |
| Yes | 492 (79.6) | 31 (75.6) | 523 (79.4) |
| Mean duration of treatment with AIT (days) | 52.5 | 37.6 | 51.6 |

\( BMI \) body mass index, \( AIT \) allergy immunotherapy tablet, \( SD \) standard deviation

\( \Delta \) Adis
Throat irritation (21.3 % of patients), paraesthesia oral (19.9 %), oral pruritus (14.0 %), ear pruritus (10.3 %) and oedema mouth (6.9 %) were recorded with the highest frequency; all other AEs were observed in less than 5 % of patients (Fig. 3).

SAEs were reported in four patients. In two patients the SAEs were unrelated to treatment (meniscus lesion and bladder surgery) and in two patients the SAEs were considered possibly related; both had started grass AIT intra-seasonally. In a 44-year-old male patient an asthma attack, dyspnoea, swollen lips and tongue, and loss of voice for 2 h was reported on day 5 of treatment and was treated with antihistamines, corticosteroids and β-sympathomimetics. In a 73-year-old female patient nausea, fainting, hypotension, bradycardia, diarrhoea, vomiting and stomach pain for less than 1 day were reported 5 h after first administration and 1.75 h after dinner. Symptoms disappeared within 2 h without treatment. In both patients the reaction was considered medically important and the patients discontinued treatment.

The results of the evaluation of the patient diary for the first 14 days of treatment are shown in Fig. 4. The rate of AEs recorded by the patients decreased continuously from 44.7 % of patients who recorded AEs on day 1 of treatment to 26.9 % with AEs on day 14. On average, about 5 % of patients reported having forgotten to take their daily tablet during the 14-day diary period.

Global tolerability was assessed as “good” or “very good” by 519 of 595 patients (87.2 %) and by the physicians in 542 of 593 patients (91.4 %) who had an evaluable assessment.

3.3 Effectiveness and Treatment Satisfaction

Effectiveness parameters could be evaluated in a total of 586 patients; 551 started treatment with grass AIT intra-seasonally.

Overall, 77.7 % of patients who started grass AIT intra-seasonally responded to treatment (as being “free of symptoms” or “improved”) with respect to nasal symptoms, 74.8 % with respect to eye symptoms, 66.4 % with respect to bronchial symptoms, and 69.0 % with respect to skin symptoms in the grass pollen season with grass AIT compared with the previous season before grass AIT. The use of symptomatic medication by patients decreased from...
79.8% in the previous season to 40.6% in the season with grass AIT. Well-being was assessed to be “better” or “much better” by 67.4% of patients who started grass AIT intra-seasonally. More than 90% of patients and physicians were “satisfied” or “very satisfied” with treatment for patients who started grass AIT intra-seasonally. The global effectiveness of treatment was assessed as “very good” or “good” by 355 of 436 patients (81.4%) and by the physicians in 386 of 450 (85.8%) patients.

4 Discussion

This study was planned to evaluate tolerability of an intra-seasonal start of treatment with grass AIT under real-life conditions. The prospective, open-label, observational design was appropriate to record data on the routine use of AIT in a real-life setting.

In this study data were recorded on 662 patients with moderate to severe rhinoconjunctivitis (including 24.6% with additional asthma) who were routinely treated with grass AIT by practising allergists. Treatment with grass AIT was started by a first administration of the tablet in the clinic in 620 patients within the grass pollen season (between June and August 2010 in Germany) and in 42 patients post-seasonally after the end of August (when the grass pollen season in Germany is over). Since the patients had not been randomly allocated to intra- or extra-seasonal start of grass AIT and the overall duration of treatment was shorter in patients who started grass AIT post-seasonally than in patients who started grass AIT within season, and due to the small number of patients with a post-seasonal start, the rates of AEs can only be compared between the two groups with limitations.

Patients were asked to enter their daily administration of grass AIT and all AEs observed in a diary for the first 14 days of treatment. The frequency of AEs recorded in the diaries was highest on day 1 of treatment and declined considerably over the course of the first 14 days of treatment (44.7% of patients with AEs on day 1, 26.9% on day 14), as was expected from the results of the controlled clinical trials with grass AIT [6–13]. The majority of patients were compliant with daily administration of the tablet; on average, only 5% forgot to take their tablet according to the diary recordings.

At first administration of grass AIT under supervision in the clinic within the grass pollen season, AEs were recorded in 34.7% of patients and were recorded in 51.6% for the entire observation period of an average 52.5 days. Most of the reactions observed in our study were of mild to moderate intensity and were severe in 8.0% of all patients treated. In two patients with an intra-seasonal start, grass AIT was discontinued due to an SAE. The most frequent reactions were local reactions at the application site in the mouth, such as throat irritation, oral paraesthesia, oral pruritus, ear pruritus and mouth oedema. This profile of reactions corresponds to the known safety profile from controlled clinical trials, as described in the Summary of Product Characteristics for GRAZAX®. Therefore, our study confirms the tolerability profile of an intra-seasonal start of grass AIT as observed in the previous placebo-controlled clinical trial [17].

Limitations of the study are those of a prospective, open-label, uncontrolled observational study. In order to minimise a potential investigator bias, sites were involved across Germany that were selected from random regional lists of allergists according to their willingness to participate. For reduction of a potential selection bias, physicians were asked to include patients in consecutive order
according to the patients consenting to be included in the study.

Due to the short period of treatment and the start of treatment within the grass pollen season, the reliability of data on effectiveness in terms of the improvement of symptoms and use of medication compared with the previous season before initiation of grass AIT is very limited and possibly biased by previous season grass pollen load and placebo effect. Nevertheless, a considerable proportion of patients considered their well-being to be already improved during the grass pollen season in which grass AIT was initiated and the rate of satisfaction with treatment was higher than 90%. This is in agreement with the early immunological effects of treatment reported by Reich et al. [17], suggesting an early effect that may already be perceived by the patient during the grass pollen season in which treatment was started. Changes from baseline in concentrations of IgE-blocking factor were significantly greater in the grass AIT-treated group than with placebo after about 9 weeks of treatment. The authors suggested that an immunomodulatory effect appears within a short period of treatment. Thus, their study results [17] were consistent with previously reported clinical trials, which show that the immunological response to grass AIT may occur early in treatment and is likely to be unaffected by the time of treatment initiation relative to the grass pollen season [6, 10, 13–15].

An evaluation of the data pooled from several trials with pre-seasonal initiation of grass AIT revealed that symptom and medication scores were significantly reduced versus placebo if the treatment period was initiated at least 8 weeks prior to the expected start of the grass pollen season, and the difference from placebo was increased if the pre-seasonal treatment period was 16 weeks, suggesting that the improvement of clinical symptoms with an intra-seasonal start in the same grass pollen season is limited [19].

In a recent analysis of immunological data from a clinical trial with subcutaneous immunotherapy, a modest but significant inverse relationship was demonstrated between post-immunotherapy serum inhibitory activity and combined symptom-rescue medication scores, whereas no such observation was made for immune-reactive IgG4 levels. This suggests that the increase of IgE-blocking factor may predict a reduction of clinical symptoms [20].

5 Conclusion

In this non-interventional, observational study the intra-seasonal start of grass AIT during routine treatment was well-tolerated, confirming the data from a previous placebo-controlled clinical trial. Our data suggest that grass AIT can be initiated within the season without compromising safety and tolerability, allowing for an immediate treatment start with SIT when the patient presents with the allergic complaints.

Acknowledgments The authors would like to thank all of the physicians who provided data on treatment of their patients for the study and Sabine Quast who provided editorial and journal submission assistance.

Funding ALK Germany sponsored this study. They were involved in trial design, data collection, analysis and interpretation. Medical writing, editorial and journal submission assistance from Sabine Quast was funded by the sponsor. J.-A. Schwab received remuneration from ALK for the documentation of patient data from his practice. J. Schnitker was funded by ALK as Clinical Research Organisation (CRO) in the study. H. Wolf and E. Wüstenberg are employees of ALK. The investigators received remuneration from ALK for the documentation of treatment of their patients. IAS GmbH received, as CRO, remuneration from ALK for its services in biometrical planning, data management and statistical analysis of the study.

Previous publication The data in this article were published in abstract form in Schwab JA, Wolf H, Schnitker J, Wüstenberg E. Verträglichkeit der SQ-standardisierten Gräser-Allergie-Immuno- therapie-Tablette und Patientenzufriedenheit bei intrasaissonalem Therapiebeginn. Allergo J 2011; 20: S45 (poster presentation at the 6th German Allergy Congress, 8–10 September 2011, Wiesbaden, Germany) and Wolf H, Schwab JA, Schnitker J, Wüstenberg E. Tolerability of the SQ-standardised grass AIT and patient satisfaction for intra-seasonal start of treatment. Allergy 2012; 67(Suppl 96):133-4 (poster presentation at the EAACI-Congress 2012, abstract no. 306).

Open Access This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and the source are credited.

References

1. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GALEN and Aller-Gen). Allergy. 2008;63(Suppl 86):8–160.
2. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J. 2004;24(5):758–64.
3. European Medicines Agency. Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases. November 2008. Publication no. CHMP/EWP/ 18504/2006. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003605.pdf Accessed 22 Jul 2013.
4. Camonica GW, Bousquet J, Casale T, et al. Sub-lingual immunotherapy: World Allergy Organization position paper 2009. Allergy. 2009;64(Suppl 91):1–59.
5. Cox L. Safety implications of different administration routes for specific immunotherapy [abstract]. J Allergy Clin Immunol. 2010; 125(2 Suppl 1): AB35.
6. Malling HJ, Lund L, Iepsen H, Poulsen L. Safety and immunological changes during sublingual immunotherapy with standardized quality grass allergen tablets. J Invest Allergol Clin Immunol. 2006;16(3):162–8.
7. Kleine-Tebbe J, Ribel M, Herold DA. Safety of a SQ-standardised grass allergen tablet for sublingual immunotherapy: a randomized, placebocontrolled trial. Allergy. 2006;61(2):181–4.
8. Calderon M, Essendrop M. Specific immunotherapy with high dose SQ standardised grass allergen tablets was safe and well tolerated. J Investig Allergol Clin Immunol. 2006;16(6):338–44.
9. Ibañez MD, Kaiser F, Knecht R, et al. Safety of specific sublingual immunotherapy with SQ standardized grass allergen tablets in children. Pediatr Allergy Immunol. 2007;18(6):516–22.
10. Durham SR, Yang WH, Pedersen MR, et al. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2006;117(4):802–9.
11. Dahl R, Kapp A, Colombo G, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablet for seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2006;118(2):434–40.
12. Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. Allergy. 2006;61(2):185–90.
13. Bufe A, Eberle P, Franke-Beckmann E, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. J Allergy Clin Immunol. 2009;123(1):167–73.
14. Dahl R, Kapp A, Colombo G, et al. Sublingual grass allergen tablet immunotherapy provides sustained clinical benefit with progressive immunologic changes over 2 years. J Allergy Clin Immunol. 2008;121(2):512–8.
15. Durham SR, Emminger W, Kapp A, et al. Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. J Allergy Clin Immunol. 2010;125(1):131–8.
16. Durham SR, Emminger W, Kapp A, de Monchy JGR, Rak S, Scadding G, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. J Allergy Clin Immunol. 2012;129(3):717–25.
17. Reich K, Gessner C, Kroker A, Schwab JA, Pohl W, Villesen H, Wüstenberg E, Emminger W. Immunologic effects and tolerability profile of in-season initiation of a standardized-quality grass allergy immunotherapy tablet: a phase III, multicenter, randomized, double-blind, placebo-controlled trial in adults with grass pollen-induced rhinoconjunctivitis. Clin Ther. 2011;33(7):828–40.
18. GRAZAX® (75,000 SQ-T oral lyophilisate) [summary of product characteristics]. Wedel: ALK; 30 Oct 2009.
19. Calderon MA, Birk AO, Andersen JS, Durham SR. Prolonged preseasonal treatment phase with Grazax sublingual immunotherapy increases clinical efficacy. Allergy. 2007;62(8):958–61.
20. Shamji MH, Ljørring C, Francis JN, et al. Functional rather than immunoreactive levels of IgG4 correlate closely with clinical response to grass pollen immunotherapy. Allergy. 2012;67(2):217–26.