

Intra-Seasonal Initiation of the SQ-Standardised Grass Allergy Immunotherapy Tablet Routinely Applied by Allergy Specialists and General Practitioners with Experience in Treatment of Allergy: A Non-Interventional Observational Study

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

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ABSTRACT

Introduction: Intra-seasonal start of treatment with the SQ[®] grass sublingual immunotherapy (SLIT) tablet (GRAZAX[®], ALK, Denmark) has been previously demonstrated to be well-tolerated. The objective of our study was to investigate the tolerability of intra-seasonal start of treatment comparing patients treated by allergists and general practitioners experienced in treatment of allergy (GPs).

Methods: In a non-interventional, open-label, observational study, data on intra-seasonal start

with the SQ[®] grass SLIT tablet were recorded in patients treated by allergists and GPs in Germany. Adverse events (AEs) were recorded by the physicians at first administration and during the 1–3-month observation period. The tablets taken and any AEs were recorded by the patients in diaries for the first 14 days.

Results: Treatment with the SQ[®] grass SLIT tablet was started in 198 patients, and in 179 intra-seasonal (allergists: 140, GPs: 39) and 19 post-seasonal; average treatment period was 47 days. AEs related to intra-seasonal start were reported in 43.6% of patients; no relevant differences between allergists and GPs were observed. In the subgroup of GPs, patients were younger ($p = 0.0191$), had more frequently asthma ($p = 0.0043$), more patients used symptomatic medication in the previous pollen season ($p = 0.0198$) and were more frequently treated for other diseases ($p = 0.0467$). In the allergists subgroup, more diagnostic allergy tests were applied ($p < 0.0001$) with less anti-allergic premedication at first administration ($p = 0.0026$).

Conclusion: The intra-seasonal start of treatment with the SQ[®] grass SLIT tablet in patients routinely treated by allergists or GPs with experience in treatment of allergy was well-tolerated, although patient characteristics were different with respect to age, frequency of asthma and concomitant allergies, use of symptomatic medication in the previous grass pollen season and concomitant treatment of

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J.-A. Schwab
Schwab and Schwab Interdisciplinary Therapy
Center, 81539 Munich, Germany

H. Wolf (✉)
Clinical Development, ALK-Abelló Arzneimittel
GmbH, 22763 Hamburg, Germany
e-mail: hendrik.wolf@alk.net

J. Schnitker
Institut für angewandte Statistik GmbH, 33647
Bielefeld, Germany

E. Wüstenberg
Medical Department, ALK-Abelló Arzneimittel
GmbH, 22763 Hamburg, Germany

E. Wüstenberg
Clinic for Otolaryngology, Universitätsklinikum
Carl Gustav Carus, 01307 Dresden, Germany

other diseases. The safety profile from a previous placebo-controlled clinical trial and data from a previous real-life study on intra-seasonal start performed by allergists were confirmed.

Keywords: Allergy immunotherapy tablet; GRAZAX®; In season; *Phleum pratense*; Rhinoconjunctivitis; Sublingual immunotherapy; Allergy immunotherapy

INTRODUCTION

The majority of patients with allergic rhinitis in response to seasonal allergens are visiting the physician's office most likely during the period of pollen exposure when symptoms and quality of life are noticeably affected. Allergy immunotherapy (AIT) as a treatment option that has the potential to modify the allergic disease [1, 2] is usually initiated after the end of the pollen season due to a presumed higher risk for side effects if allergens for therapy are administered while the patient is naturally exposed. In a recently published systematic review of the published literature on coseasonal initiation of treatment with AIT, no increase of the risk of systemic, serious or severe reactions was identified with subcutaneous (SCIT) and sublingual immunotherapy (SLIT) [3].

The standardised sublingual grass allergy immunotherapy tablet (SQ® grass SLIT tablet) has been developed for sublingual application in patients with grass pollen-induced rhinoconjunctivitis, and has been investigated in more than 5700 patients in controlled clinical trials in Europe and North America [4–18]. It has been approved Europe-wide and was launched in Germany in November 2006.

The safety, tolerability, data on adherence, effectiveness and health-related quality of life have been investigated in several non-interventional, observational studies with the SQ® grass SLIT tablet in real-life application by allergists in Germany, including a study on intra-seasonal initiation of treatment with more than 600 patients [19–22] that confirmed results from a previous Randomized double-blind placebo-control (RDBPC) trial [18]. A cohort study, including all German National Health

beneficiaries insured by the German health insurance provider AOK PLUS (Saxony) from 2005 to 2011, revealed a proportion of 36.2% of adult patients with allergic rhinitis treated exclusively by general practitioners, and a proportion of 21.2% of children [23]. Only a small proportion of general practitioners is experienced in treatment of allergy, including AIT and, thus, is able to offer his/her patients AIT as a treatment option. AIT is currently applied in Germany mostly by allergists of the ear-nose-throat (ENT), dermatology and pulmonology disciplines.

The objective of our study was to investigate the tolerability and patient characteristics in patients treated by allergists and general practitioners with experience in treatment of allergy in Germany who initiated treatment with the SQ® grass SLIT tablet intra-seasonally.

METHODS

Study Design and Treatment

In this non-interventional, open-label, uncontrolled, observational, multi-centre study, the treatment of patients who started administration of the SQ® grass SLIT tablet within the grass pollen season in summer 2014 (June–August) or 2015 (May–August) in Germany was documented by 37 allergists and 15 general practitioners with experience in treatment of allergy including AIT (GPs), distributed across Germany. Centres were asked to record data on 2–3 patients in a 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 potentially eligible patients in a patient log. Patients were asked to record the application of the tablet and any adverse events (AEs), and their medication, if applicable, during the first 14 days of treatment at home. The diary period was limited to the first 14 days because it is known from the controlled trials with the SQ® grass SLIT tablet that AE incidences are highest on day 1 of treatment and subsequently decline with proceeding treatment [4–11].

Allergy Immunotherapy

Patients were treated with the SQ[®] grass SLIT tablet [GRAZAX[®], *Phleum pratense* 75,000 SQ-T/2, 800 bioequivalent allergy units (BAU), ALK-Abelló A/S, Hørsholm, Denmark]. First administration was applied in the physician's office and treatment was then continued by the patient by daily intake of the tablet at home. Treatment period under observation of the study comprised the first 1–3 months of treatment, depending on the description of 30 or 100 tablets after the first administration.

Ethics and Data Protection

According to German drug law, the authorities have to be notified of non-interventional post-marketing studies. The study was approved by the Ethics Committee of the Landesärztekammer Baden-Württemberg (reference no. F-2014-50) and the consent of the patients for collection of their data was obtained. The decision of the physician to prescribe SLIT with the SQ[®] grass SLIT tablet was taken independently from the inclusion of the patient in the study. For recording and evaluation of data, patients were assigned a three-digit patient number. Direct identification of the patients was restricted to the physicians' offices that participated in the study.

Patients

Data on patients with a diagnosis of grass pollen-induced rhinitis and/or conjunctivitis (according to symptoms, skin prick test or specific IgE in blood serum), with or without asthma, and with clinically relevant symptoms, who had no contraindications to a prescription of the SQ[®] grass SLIT tablet according to the Summary of Product Characteristics for GRAZAX[®] [24], and who were starting treatment with the SQ[®] grass SLIT tablet within the grass pollen season, were eligible to be documented in this study. Contraindications included hypersensitivity to any of the excipients of the SQ[®] grass SLIT tablet, 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; patients with uncontrolled or severe asthma (forced expiratory volume in 1 s [FEV₁] < 70% of predicted value after adequate pharmacologic treatment in adults and < 80% in children).

Assessments

Patients were included in the study at visit 1 (V1). At V1, data on demographics, allergy history, including age at first appearance of symptoms, clinical manifestations of the allergy (rhinitis/conjunctivitis/asthma/atopic dermatitis), other allergies, diagnostics performed, any previous treatment by AIT, concomitant treatments by AIT or other medications due to concomitant diseases, and symptoms and medication use in the previous grass pollen season were recorded. A study diagram with the main assessments is shown in Fig. 1.

The severity of nasal, ocular, bronchial and skin symptoms was rated on a scale of 0–3 (no/mild/moderate/severe symptoms), and symptomatic medication was recorded (topical or oral antihistamines/nasal or oral corticosteroids/inhaled corticosteroids/inhaled short-acting β_2 agonists (SABA)/inhaled long-acting β_2 agonists (LABA)/other, to be specified). At first administration of the SQ[®] grass SLIT tablet in the clinic, anti-allergic pre-medication, if used, was recorded and any AEs that occurred while the patient was under surveillance of tolerability for 30 min. An AE was defined as any untoward medical occurrence in a patient who administered the SQ[®] grass SLIT tablet 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 record the administration of the SQ[®] grass SLIT tablets and any AEs in a diary, including actions taken due to AEs (e.g., medication taken/physician called or visited). AEs were specified by the physician in the case report form (CRF) as diagnosis or

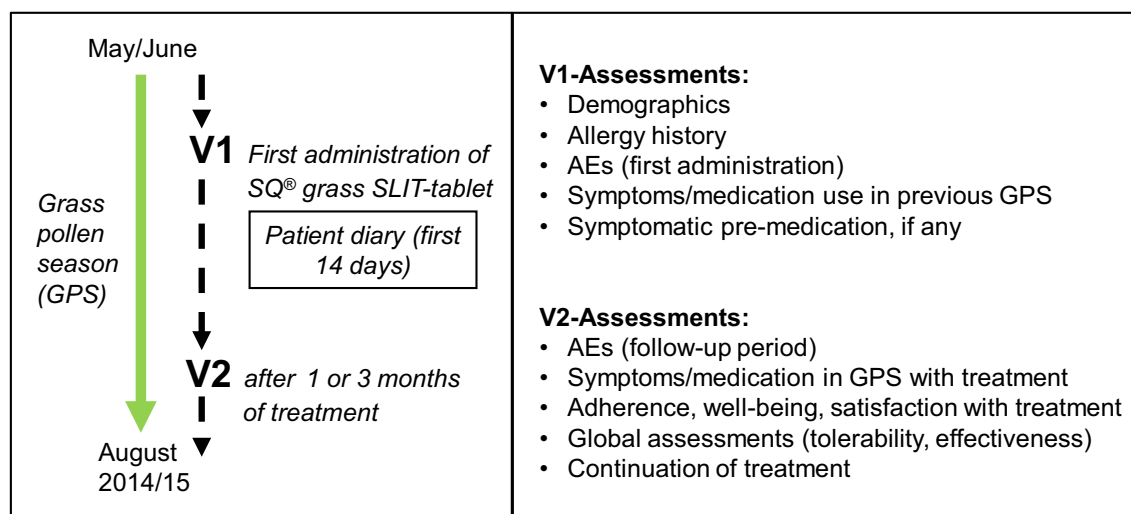


Fig. 1 Study diagram. Treatment was started by first administration of the SQ[®] grass SLIT tablet in the physician's office during the grass pollen season in summer 2014 (June–August) or 2015 (May–August) in Germany at V1 and continued by daily administration of the tablet by the patient at home. Patients were followed-up after 1

or 3 months of treatment at V2, depending on the prescription of 30 or 100 tablets at V1. Daily administration of the tablets and any AEs were recorded by the patients in diaries for the first 14 days of treatment. *AE* adverse event, *GPS* grass pollen season, *SLIT* sublingual immunotherapy, *V* visit

description, and assessed by intensity (mild/moderate/severe), causality (possible/unlikely), change of treatment (no change/interruption/discontinuation), treatment by medication (if applicable), outcome (recovered/recovered with sequelae/not recovered/fatal/unknown) and seriousness (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, was a congenital abnormality or birth defect, or any other event judged medically important.

At V2 after 1–3 months of treatment (according to previous prescription of either 30 or 100 SQ[®] grass SLIT tablets), the patients returned to the physician's office to have their prescription renewed. The physician then interviewed the patients about AEs that had occurred between V1 and V2 during home treatment, and recorded all AEs in the CRF, together with his/her medical assessment. Furthermore, the overall adherence to treatment of

the patient during the observation period was assessed by the physician according to rates of < 50%, 50–79% or ≥ 80%; with a rate of 80% or higher, the patient was considered to be adherent. Symptoms and medication use after 1–3 months of treatment with the SQ[®] grass SLIT tablet were recorded and the well-being of the patient with the SQ[®] grass SLIT tablet compared to previous years was assessed (much better/better/unchanged/worse/much worse). Patients and physicians rated their satisfaction with treatment by the SQ[®] grass SLIT tablet (very satisfied/satisfied/dissatisfied/very dissatisfied), and globally assessed the tolerability (very good/good/moderate/poor) and overall effectiveness of therapy (very good/good/moderate/no effect/not assessable). Finally, it was recorded whether the patient continued or discontinued treatment, and reasons for discontinuation.

Statistics

Data analysis was performed primarily by descriptive statistics, using minimum, maximum, median, mean and standard deviation for

continuous data, as well as frequency distributions for ordinal data. No imputation was performed in case of missing data, but all available data were used to their full extent. The principal statistical software used was SAS[®], version 9.3. No formal sample size calculation was made for this study. The primary objective was to record data on safety and tolerability of the SQ[®] grass SLIT tablet when treatment was started intra-seasonally and to compare subgroups of patients treated by allergists and GPs.

In the all-patients-treated set of the study, the patients were classified as 'intra-seasonal' (June–August 2014/May–August 2015) or 'post-seasonal' (September 2014/15 or later) with respect to their start of treatment, and the

respective data were presented separately. Reasons for premature termination were non-adherence, AEs, medical reasons, insufficient effectiveness, improvement or other reasons. 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 with respective entries in the CRFs.

Subgroups of patients treated by allergists and GPs were compared by analytical statistical test procedures (*U* test and χ^2 test).

Table 1 Patient characteristics for patients with intra-seasonal and post-seasonal start of treatment, and for all patients treated

	Start of treatment		All patients treated (<i>n</i> = 198)
	Intra-seasonal (<i>n</i> = 179)	Post-seasonal (<i>n</i> = 19)	
Median age, years	30.0	31.0	30.0
Range, years	6–75	20–57	6–75
Patients < 18 years, <i>n</i> (%)	13 (7.3)	–	13 (6.6)
Sex, <i>n</i> (%)			
Male	84 (46.9)	10 (52.6)	94 (47.5)
Female	95 (53.1)	9 (47.4)	104 (52.5)
BMI (kg/m ²), mean $\pm$ SD	24.7 $\pm$ 4.8	25.5 $\pm$ 4.3	24.8 $\pm$ 4.8
Symptoms in the previous season, <i>n</i> (%)			
Moderate-to-severe nasal symptoms	158 (88.3)	16 (84.2)	174 (87.9)
Moderate-to-severe eye symptoms	132 (73.7)	13 (68.4)	145 (73.2)
Asthma, <i>n</i> (%)	39 (21.8)	–	39 (19.7)
Allergy history			
Mean duration ($\pm$ SD) since diagnosis of grass pollen allergy, years	5.7 $\pm$ 8.4	14.3 $\pm$ 10.9	6.5 $\pm$ 9.0
History of immunotherapy, <i>n</i> (%)	16 (8.9)	3 (15.8)	19 (9.6)
Symptomatic medication taken during previous season, <i>n</i> (%)	119 (66.5)	16 (84.2)	135 (68.2)
Duration of treatment with AIT, mean days $\pm$ SD	47 $\pm$ 34	48 $\pm$ 67	47 $\pm$ 38

BMI body mass index, AIT allergy immunotherapy, SD standard deviation, "–" no patient fulfilled the characteristic

RESULTS

Patients

Data for a total of 198 patients could be evaluated, of which 179 patients started treatment as planned during the grass pollen season with the SQ[®] grass SLIT tablet and 19 patients post-season (later than August). Therefore, the data for patients with an intra-seasonal start (until 31 August 2014/15, $n = 179$; 90.4%) and post-seasonal start of treatment (after 31 August 2014/15, $n = 19$; 9.6%) were stratified into two subgroups; 140 patients were treated by 37 allergists, and 39 by 15 GPs. Average treatment period for patients with an intra-seasonal start of treatment with the SQ[®] grass SLIT tablet was 47 ± 34 days. The patients' demographic data at start of grass AIT (V1) are summarised in Table 1.

After the first administration in the physician's office, nine patients did not return for the follow-up visit. Treatment was discontinued during the observation period in a total of 25 patients (12.6%), and in 20 patients within the

first 14 days of treatment. Diaries were evaluable for 150 (75.8%) patients and in 144/179 (80.4%) patients with an intra-seasonal start of treatment. The flow of patients through the study is shown in Fig. 2.

Patients Treated by Allergists and General Practitioners

Data on patient characteristics, diagnostic testing and concomitant medication in patients treated by allergists and GPs are displayed in Table 2.

Statistically significant differences of patient characteristics were observed with respect to mean age of the patients (allergists: 34.1 ± 13.4 of patients vs. GPs: 28.8 ± 14.4 ; $p = 0.0191$), bronchial asthma (allergists: 17.1% vs. GPs: 38.5%; $p = 0.0043$), concomitant type I allergies (allergists: 48.6% vs. GPs: 69.2%; $p = 0.0223$) and symptomatic medication used in the previous grass pollen season (allergists: 62.1% vs. 82.1%; $p = 0.0198$). The number of patients who had previously been tested for grass pollen allergy was higher in patients treated by

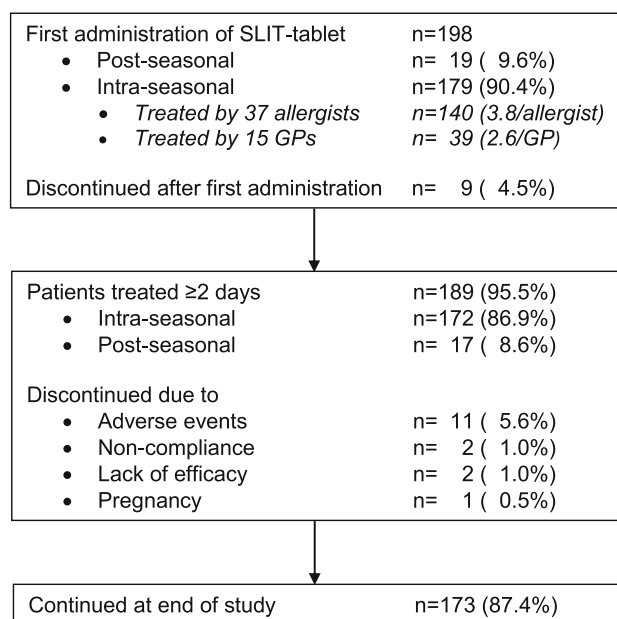


Fig. 2 Flow of patients. GP general practitioner with experience in allergy treatment, SLIT sublingual immunotherapy

Table 2 Comparison of patient characteristics in patients with intra-seasonal treatment start treated by allergists and general practitioners with experience in treatment of allergy (GPs)

	Patients treated by Allergists (<i>n</i> = 140) <i>n</i> (%)	Patients treated by GPs (<i>n</i> = 39) <i>n</i> (%)	<i>p</i> value
Age (years), mean $\pm$ SD	34.1 $\pm$ 13.4	28.8 $\pm$ 14.4	0.0191 (<i>U</i> test)
Rhinitis	136 (97.1)	38 (97.4)	0.9218 (χ^2 test)
Conjunctivitis	113 (80.7)	30 (76.9)	0.6014 (χ^2 test)
Bronchial asthma, <i>n</i> (%)	24 (17.1)	15 (38.5)	0.0043 (χ^2 test)
Atopic dermatitis	11 (7.9)	6 (15.4)	0.1562 (χ^2 test)
Other	18 (12.9)	2 (5.1)	0.1754 (χ^2 test)
Concomitant type I allergies	67 (48.6)	27 (69.2)	0.0223 (χ^2 test)
At least one diagnostic test to grass	126 (90.0)	24 (61.5)	< 0.0001 (χ^2 test)
Symptomatic medication in previous GPS	87 (62.1)	32 (82.1)	0.0198 (χ^2 test)
Concomitant treatment of other diseases	8 (5.7)	6 (15.4)	0.0467 (χ^2 test)
Anti-allergic premedication at initiation	4 (2.9)	6 (15.4)	0.0026 (χ^2 test)

GP general practitioners with experience in treatment of allergy, *GPS* grass pollen season

allergists (90.0% of patients vs. 61.5% of patients treated by GPs), while the proportion of patients who received a concomitant treatment of other diseases was higher in GPs (allergists: 5.7% vs. GPs: 15.4%; $p = 0.0467$), and also the proportion of patients who received an anti-allergic premedication at first administration of the SQ[®] grass SLIT tablet (allergists: 2.9% vs. GPs: 15.4%; $p = 0.0026$; see Table 2).

Safety and Tolerability

During the entire observation period, AEs were observed in 84 (42.4%) of the 198 total patients: in 81/179 (45.3%) patients who started grass AIT intra-seasonally, and in 3/19 (15.8%) patients who started grass AIT post-season (Table 3). AEs in patients with intra-seasonal start of treatment were observed in 21/39 (53.8%) patients treated by GPs and 60/140 (42.9%) treated by allergists during the entire

observation period; the difference was not statistically significant (Table 4).

After first administration of the SQ[®] grass SLIT tablet, AEs were recorded in 61/198 (30.8%) patients treated in total, and in 59/179 (33.0%) patients with intra-seasonal start and 2/19 (10.5%) patients with post-seasonal start (Table 3).

Most AEs were assessed as possibly related to the SQ[®] grass SLIT tablet, and were, thus, ADRs. The majority of the ADRs were of mild or moderate intensity. In patients with intra-seasonal start of treatment with the SQ[®] grass SLIT tablet, severe reactions were recorded in 9 (5.0%) cases; 7.8% of patients were treated with medication and 4.5% discontinued treatment due to ADRs (Table 3).

ADRs on the first day of treatment were observed in 12/39 (30.8%) patients treated by GPs and 45/140 (32.1%) treated by allergists, and during the entire observation period in 20/39 (51.3%) patients treated by GPs and

Table 3 Adverse events and adverse drug reactions in patients with intra-seasonal and post-seasonal start of treatment, and in all patients treated

	Start of treatment		All patients treated (<i>n</i> = 198)
	Intra-seasonal (<i>n</i> = 179)	Post-seasonal (<i>n</i> = 19)	
Patients analysed, <i>n</i> (%)			
With first intake in the clinic	179 (100.0)	19 (100.0)	198 (100.0)
With > day 1 of treatment	172 (96.1)	17 (89.5)	189 (95.5)
With evaluable diaries	144 (80.4)	6 (31.6)	150 (75.8)
AEs, <i>n</i> (%), <i>E</i>			
On first treatment day	59 (33.0), 124	2 (10.5), 6	61 (30.8), 130
During entire course of treatment	81 (45.3), 400	3 (15.8), 30	84 (42.4), 430
Treated by medication	16 (8.9), 91	1 (5.3), 3	17 (8.6), 94
ADRs, <i>n</i> (%), <i>E</i>			
On first treatment day	57 (31.8), 119	2 (10.5), 6	59 (29.8), 125
During entire course of treatment	78 (43.6), 372	3 (15.8), 30	81 (40.9), 402
Severity, mild	57 (31.8), 303	–, 20	57 (28.8), 323
Moderate	12 (6.7), 41	–, 1	12 (6.1), 42
Severe	9 (5.0), 28	3 (15.8), 9	12 (6.1), 37
Treated by medication	14 (7.8), 88	1 (5.3), 3	15 (7.6), 91
Leading to discontinuation	8 (4.5), 28	2 (10.5), 7	10 (5.1), 35

AE adverse event, *ADR* adverse drug reaction, *E* number of events, “–” no patient fulfilled the characteristic

58/140 (41.4%) treated by allergists; all differences were not statistically significant (Table 4).

Throat irritation (17.3% of patients), paraesthesia oral (15.6%), oral pruritus (9.5%) and ear pruritus (8.4%) were the most frequently recorded MedDRA preferred terms (PTs) with intra-seasonal start of treatment. All other ADRs were observed in less than 5% of patients (Table 5). No SAEs were reported.

The average rate of AEs recorded by the patients with intra-seasonal start of treatment in the diaries decreased continuously from 38.4% of patients who recorded AEs on day 1 of treatment to 20.0% on day 14; 2.8% of patients used a medication due to AEs during the first 14 days of treatment.

Global tolerability was rated ‘good’ or ‘very good’ in 153/169 (90.5%) of patients’

assessments, and 155/170 (91.2%) of physicians’ assessments in patients with intra-seasonal start of treatment that had been documented for ≥ 2 days.

Effectiveness and Treatment Satisfaction

Effectiveness parameters could be evaluated in a total of 172 patients with intra-seasonal start of treatment with the SQ[®] grass SLIT tablet.

Compared with the previous season before starting AIT, 79.3% of these patients responded to treatment (as being ‘free of symptoms’ or ‘improved’) with respect to nasal symptoms, 75.7% with respect to eye symptoms, 68.0% with respect to bronchial symptoms and 62.5% with respect to skin symptoms in the first grass

Table 4 Adverse events and adverse drug reactions in patients with intra-seasonal start of treatment treated by allergists and general practitioners with experience in treatment of allergy (GPs)

	Patients treated by allergists (<i>n</i> = 140) <i>n</i> (%)	Patients treated by GPs (<i>n</i> = 39) <i>n</i> (%)	<i>p</i> value
AEs at first administration of SLIT tablet	46 (32.9)	13 (33.3)	0.9554 (χ^2 test)
ADRs at first administration of SLIT tablet	45 (32.1)	12 (30.8)	0.8706 (χ^2 test)
AEs during entire observation period	60 (42.9)	21 (53.8)	0.2227 (χ^2 test)
ADRs during entire observation period	58 (41.4)	20 (51.3)	0.2724 (χ^2 test)

AE adverse event, *ADR* adverse drug reaction, *GP* general practitioners with experience in treatment of allergy

pollen season with treatment by the SQ[®] grass SLIT tablet. The proportion of patients who used symptomatic medication decreased from 65.7% in the previous season to 34.9% in the first season with treatment by the SQ[®] grass SLIT tablet. Well-being was assessed to be 'better' or 'much better' by 74.3% of patients with intra-seasonal start of treatment, and 94.1% of patients and 92.9% of physicians rated to be 'satisfied' or 'very satisfied' with the intra-seasonal start of treatment with the SQ[®] grass SLIT tablet. The global effectiveness of treatment was rated 'very good' or 'good' in patients with intra-seasonal start of treatment by 131/153 (85.6%) patients, and by the physicians in 139/156 (89.1%) patients.

Table 5 ADRs in $\geq 5\%$ of patients in any of the groups in patients with intra-seasonal and post-seasonal start of treatment, and in all patients treated

MedDRA system organ class MedDRA preferred term	Start of treatment		All patients treated (<i>n</i> = 198) <i>n</i> (%), <i>E</i>
	Intra-seasonal (<i>n</i> = 179) <i>n</i> (%), <i>E</i>	Post-seasonal (<i>n</i> = 19) <i>n</i> (%), <i>E</i>	
All patients with ADRs	78 (43.6), 372	3 (15.8), 30	81 (40.9), 402
Ear and labyrinth disorders	16 (8.9), 33	–	16 (8.1), 33
Ear pruritus	15 (8.4), 30	–	15 (7.6), 30
Gastrointestinal disorders	59 (33.0), 166	3 (15.8), 11	62 (31.3), 177
Oral pruritus	17 (9.5), 29	1 (5.3), 1	18 (9.1), 30
Oedema mouth	8 (4.5), 12	1 (5.3), 1	9 (4.5), 13
Paraesthesia oral	28 (15.6), 51	–	28 (14.1), 51
Respiratory, thoracic and mediastinal disorders	40 (22.3), 128	2 (10.5), 11	42 (21.2), 139
Throat irritation	31 (17.3), 80	1 (5.3), 4	32 (16.2), 84

ADR adverse drug reaction, *E* number of events, *MedDRA* Medical Dictionary for Drug Regulatory activities, "–" no patient fulfilled the characteristic

Adherence

The estimated rate of adherence to taking the tablet daily was assessed by the physicians as $\geq 80\%$ in 154/172 (89.5%) patients, as 50–79% in 8 (4.7%) and $< 50\%$ in 10 (5.8%) patients with intra-seasonal start of treatment (all patients treated: 89.9%, 4.8% and 5.3%, respectively).

Overall, diaries for the first 14 days of treatment were returned by 150 patients and were kept over 14 days by 148 patients (1 patient over

11 days, and 1 patient over 4 days). On average, 4.1% of patients reported to have forgotten to take the tablet or had missing entries during the 14-day diary period (between 2.7% and 4.1%, with two exceptions of 6.0% and 10.1%).

DISCUSSION

According to a systematic review of the published literature on intra-seasonal initiation of AIT, no increase of AEs of concern was observed with SCIT and SLIT [3].

The feasibility and good tolerability of an intra-seasonal initiation of AIT with the SQ[®] grass SLIT tablet has been shown in a previous RDBPC trial and was confirmed by a large non-interventional study in real life [18, 19].

In the current study we investigated the tolerability of the intra-seasonal start with the SQ[®] grass SLIT tablet in the real-life setting during the first 1–3 months of treatment when applied by allergists and by GPs. Tolerability was assessed by the physician at first administration of the tablet in the clinic, and AEs and tablet applications were recorded by the patient in diaries for the first 14 days of treatment. Overall adherence was assessed by the physician at the end of the observation period. Assessments of symptoms and medication use and patient's well-being were compared with retrospective assessments for the previous grass pollen season. AIT with the SQ[®] grass SLIT tablet was initiated within the grass pollen season in 90.4% of patients and in 9.6% post-season. Patients were, therefore, stratified into the subgroups with intra-seasonal and post-seasonal start of treatment. Since the patients were not randomly allocated to an intra-seasonal or post-seasonal treatment start, and due to the small number of patients with post-seasonal start, a comparison of the incidences of AEs of the two groups may be misleading. Moreover, in a previous real-life study with post-seasonal start of treatment that included a much larger number of patients, higher incidences of AEs were observed with post-seasonal start of treatment than in the current study [21]. ADRs with intra-seasonal start of treatment with the SQ[®] grass SLIT tablet were recorded overall in 43.6% of

patients, and in 31.8% at first administration of the tablet, and were classified in 38.5% of patients as mild-to-moderate and in 5% as severe. ADRs were treated by medication in 7.8% of patients and led to discontinuation in 4.5%. The overall rate of ADRs in patients whose treatment with the SQ[®] grass SLIT tablet was initiated intra-seasonally was slightly lower in this study compared to the previous observational study (43.6% vs. 49.2% of patients) [19], but otherwise the safety results were very similar. An improvement of symptoms in the season of treatment initiation was reported by 79.3% of patients, the number of patients who used symptomatic medication decreased, and patients' well-being was perceived to be improved by 74.3% of patients. The adherence with daily intake of the tablet was $\geq 80\%$ in 89.5% of patients according to the physicians' assessment.

The intra-seasonal initiation of treatment with the SQ[®] grass SLIT tablet in this study was recorded in 140 patients by 37 allergists and in 39 patients by 15 GPs, resulting in average treatment rates of 3.8 patients for allergists and 2.6 for GPs. The number of GPs with experience in treatment of allergy, and especially in using AIT, is limited in Germany [23], and thus, the number of GPs participating in this study. The number of patients treated by GPs was lower than the number of patients treated by allergists.

No statistically significant differences in ADRs were observed between patients treated by allergists and GPs at first administration of the SQ[®] grass SLIT tablet and during the entire observation period of the study, although patient groups treated by allergists and GPs were observed to differ in some characteristics: the proportion of patients treated by GPs was significantly higher compared to allergists for concomitant bronchial asthma, concomitant type I allergies, symptomatic medication used in the previous grass pollen season before initiation of AIT, concomitant treatment due to other diseases and patients who received a pre-medication by antihistamines at first administration of the SQ[®] grass SLIT tablet. The mean age of the patients and the number of diagnostic tests to identify grass pollen allergy were,

however, higher in patients treated by allergists. Nevertheless, the results of this study confirm the results of a previous RDBPC clinical trial [18] and a non-interventional study [19] that have demonstrated intra-seasonal initiation of treatment with the SQ[®] grass SLIT tablet to be feasible and well-tolerated.

The study has limitations due to its open-label, un-controlled and observational design. Patients were involved by sites distributed over Germany. For reduction of a potential selection bias, physicians were asked to include patients in a consecutive order, according to the consent of the patients. A source of potential bias with respect to the effectiveness assessments is the natural variability of grass pollen exposure in Germany during the observation period of the study and the previous grass pollen season.

In conclusion, the intra-seasonal start of treatment with the SQ[®] grass SLIT tablet in patients routinely treated by allergists or GPs was well tolerated, although patient characteristics were different with respect to age, proportions of patients with asthma and concomitant allergies, symptomatic medication use in the previous grass pollen season and concomitant treatment of other diseases. The results confirm the safety profile from a previous placebo-controlled clinical trial and data from a previous real-life study on intra-seasonal initiation of treatment with the SQ[®] grass SLIT tablet.

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Compliance with ethical guidelines. The study was approved by the Ethics Committee of the Landesärztekammer Baden-Württemberg (reference no. F-2014-50) and all procedures followed were in accordance with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

Data availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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