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Real-life safety of 5-grass pollen tablet in 5-to-9-year-old children with allergic rhinoconjunctivitis

Michael Gerstlauer, MD [*]; Zsolt Szepfalusi, MD [†]; David Golden, MD [‡]; Bob Geng, MD [§]; Jacques de Blic, MD, PhD [¶]

[*] Pediatric Pneumology and Allergology unit, Medical University of Augsburg, Augsburg, Germany
[†] Department of Pediatrics, Medical University of Vienna, Vienna, Austria
[‡] Allergy & Immunology, Medstar Franklin Square Medical Center, Baltimore, Maryland
[§] Divisions of Adult and Pediatric Allergy and Immunology, Rady Children's Hospital Severe Asthma Clinic, University of California, San Diego, California
[¶] Pediatric Pneumology and Allergology unit, Necker-Enfants Malades Hospital, Paris, France; Université Paris Descartes, Paris, France

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ABSTRACT

Background: Although 5-grass pollen sublingual immunotherapy has a good safety profile in controlled clinical trials, additional safety information among pediatric patients in a real-world setting would be useful.
Objective: To further document the safety of 5-grass tablet among children aged 5 to 9 years with allergic rhinoconjunctivitis (ARC).
Methods: This multicenter, observational study included allergy immunotherapy-naïve 5- to 9-year-old children with grass pollen–induced ARC prescribed with 5-grass tablet daily (3-day dose escalation to 300 index of reactivity [IR]). Patients were followed up daily for safety and tolerability over the first 30 treatment days. Adverse events (AEs) and adverse drug reactions (ADRs) were analyzed descriptively.
Results: Three hundred seven children (mean age, 7.1 years) were enrolled. Fifty-eight percent were confirmed as polysensitized, and 36% had mild-to-moderate asthma. Of 307 patients, 233 (76%) reported AEs, and 173/307 (56%) reported ADRs, most frequently mild application-site reactions (throat irritation, oral pruritus, oral paresthesia). Sixteen of 307 (5.2%) patients withdrew because of ADRs. In 143 of 173 (83%) patients, ADRs first occurred within 1 week of starting treatment. More than half of the ADRs lasted less than 2 days, and ADRs resolved spontaneously in 161 of 173 (93%) patients. Recurrences of ADRs were reported in 45 of 173 (26%) patients and were also mainly application-site reactions. No notable differences were found in ADRs related to whether patients had asthma at inclusion. Neither epinephrine use nor admission to intensive care unit was reported.
Conclusion: The safety profile of 5-grass tablet in pediatric ARC patients aged 5 to 9 years was consistent with safety findings in older patients, most ADRs being at the application site and mild to moderate. ClinicalTrials.gov identifier: NCT02295969; EUPAS registration number: 8104.

Introduction

Allergic rhinoconjunctivitis (ARC) is a very common chronic inflammatory disease of the upper airways, characterized by symptoms such as nasal congestion, rhinorrhea, sneezing, itching, and also itchy-watery eyes.[1] The disease has an estimated worldwide prevalence of 15% to 25%,[2] carrying a high global burden particularly among children and adolescents.[2,3]

Rhinoconjunctivitis symptoms in children show an average worldwide prevalence of 8.5% (range, 4.2%-12.7%) in 6- to 7-year-olds, increasing to 14.6% (range, 1.0%-45.1%) in 13- to 14-year-olds.[4] Several factors may underlie these high prevalence figures,

Reprints: Dr. Michael Gerstlauer, Klinik für Kinder und Jugendliche am Klinikum Augsburg, Stenglinstr. 2, 86154 Augsburg, Germany; E-mail: Michael.Gerstlauer@uk-augsburg.de.
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including increased and earlier exposures to allergens, irritants, and pollutants.[2] The main mechanism causing the symptoms of ARC is the immunoglobulin E (IgE)–mediated immune response to environmental allergens resulting in mucosal inflammation of the upper respiratory airways and eyes.[5–7] Disease-triggering antigens are varied but most commonly include grass pollen and house dust mites,[2] and 28% to 41% of patients have been reported to be allergic or sensitized to these allergens.[8,9] If left unmanaged, moderate-to-severe symptoms of ARC cause disturbances in sleep,[10–12] and the consequent daytime fatigue and somnolence can negatively impact quality of life[13] and school performance.[14] Furthermore, ARC is associated with an increased risk or worsening of allergic asthma.[1,15,16]

Symptoms of ARC are controlled mainly by pharmacologic agents, including intranasal corticosteroids, and oral and intranasal antihistamines.[15,17,18] However, these therapies may not be effective in all patients,[19] and symptom remission does not occur very often.[20,21] Furthermore, there may be parental concerns over the potential systemic side effects of corticosteroids in pediatric patients (including growth effects and cortisol suppression) as well as the sedative and anticholinergic side effects of antihistamines.[21–23]

Allergy immunotherapy for ARC is currently the only form of treatment with proven long-term efficacy and potential disease-modifying effect.[24,25] Subcutaneous immunotherapy in pediatric patients is restricted because of the inconvenience of administration and safety concerns.[26,27] However, the development of sublingual immunotherapy (SLIT) provides a more convenient means of administration for children and can potentially prevent progress of the allergic disease process if introduced at an early age.[28,29]

Two commercial grass-pollen extract SLIT tablets are available: 5-grass, and timothy-grass formulations.[30] These are authorized for treatment of ARC in patients of 5 years and older in many countries worldwide. Both have shown clinical efficacy (in terms of symptom reduction) in randomized controlled trials recruiting pediatric ARC patients.[31–33] Moreover, the 5-grass and timothy-grass formulations had a similar safety profile in the child and adolescent subpopulations.[32,33]

Although SLIT has a good safety profile in controlled clinical trials, more information from the real-world setting on this therapy among pediatric patients would still be useful to further characterize its safety profile. In April 2014, 5-grass SLIT tablet was granted marketing approval for use in “patients with grass-pollen-induced allergic rhinitis with or without conjunctivitis aged 10 through 65 years” by the US Food and Drug Administration, which requested (under the Pediatric Research Equity Act) a post-marketing study to be conducted in grass-pollen–allergic children aged 5 to 9 years. The aim of this study was thus to further describe the safety and tolerability of 5-grass tablet in allergic patients of this age class under normal conditions of use. We present here the findings of this large international observational study.

Methods

Study Design and Patients

This study (registration numbers: NCT02295969, EUPAS8104) was a multicenter, international (France, Germany, and Austria), post-marketing observational study recruiting allergy immunotherapy-naïve children aged 5 to 9 years with grass pollen–induced allergic rhinitis with or without conjunctivitis, prescribed daily SLIT with a 5-grass allergen tablet (Oralair, Stallergenes Greer, Antony, France). Before study procedures were initiated for use with any patient, written informed consent was given by the parent or legal guardian confirming their willingness to participate and involve their child in the study. Patient recruitment was performed during the planned visit to the allergist/physician, after prescription of 5-grass tablet. Prescription of 5-grass tablet was independent from the decision to include the patient in the study and in accordance with the product labeling. Patients were not included if they had any of the contraindications stated in the product labeling, if they were already participating in another clinical trial, or if their parent/guardian was unable to complete a daily record card. Before starting the study, the protocol, informed consent form, patient information sheet, and any other relevant study documentation were reviewed and approved when applicable by a regulatory body or Independent Ethics Committee in accordance with the local legal requirements.The study was conducted in accordance with the principles of the Declaration of Helsinki, and good clinical practice guidelines, including the International Council for Harmonization: ICH E6, the European Medicines Agency (EMA): Good Pharmacovigilance Practices, the US Food and Drug Administration: 21.CFR.312, and the applicable local laws and regulations.

Immunotherapy

The SLIT tablets used (Oralair, Stallergenes Greer, Antony, France), containing freeze-dried allergen extract of 5 grass pollens (cocksfoot/orchard [*Dactylis glomerata*], sweet vernal grass [*Anthoxanthum odoratum*], rye grass [*Lolium perenne*], meadow grass/Kentucky blue [*Poa pratensis*], and timothy [phleum pratense]), were available at dose strengths of 100IR (Index of Reactivity) and 300IR. The Index of Reactivity or “IR” is a Stallergenes In-House Reference Standard for the measurement of the total allergenic activity, per the European Medicines Agency guideline on allergen products of November 20, 2008 (EMEA/CHMP/BWP/304831/2007) and the European Pharmacopoeia on allergen products (01/2012:1063).[33,34]

In accordance with the product labeling, treatment was to begin approximately 4 months before the expected onset of the grass-pollen season and continue throughout the season. Dosage was increased by 100IR over the first 3 days to reach 300IR, which was the daily dose recommended for the duration of treatment. The patient took the first dose under medical supervision of the prescribing physician and was monitored for at least 30 minutes per real-world clinical practice. Subsequent doses were taken under parent/guardian supervision. Treatment was contraindicated in patients with severe, unstable, or uncontrolled asthma.

Procedures and Study Assessments

The study was performed between January 2015 and February 2017 with 3 patient recruitment periods before the 2015, 2016, and 2017 pollen seasons. There was a study initiation visit, a telephone call at Day 4 of treatment, and a follow-up appointment at 31 to 45 days after the initiation visit (Fig 1A). Safety and tolerability were evaluated for the first 30 treatment days.

At the initiation visit, the patient’s treating allergist/physician recorded details of the patient’s medical history, including demographic information, allergy history, any concomitant medications, date of onset of ARC, and any results of cutaneous tests (for tested allergens) or in vitro testing for specific immunoglobulin E (IgE) to grass pollen. Any adverse event (AE) associated with the first intake of 5-grass tablet was also recorded at the initiation visit.

A daily record card was given to the parent/guardian at the start of treatment. Throughout the study, the parent/guardian recorded daily the date and time of 5-grass tablet intake, any AE, and any use of concomitant medication. In cases of treatment discontinuation, the reason for discontinuation was also recorded. At day 4, the physician called the parent/guardian to ask whether the medicinal product was being taken, whether the patient had had any AEs or had taken concomitant medication, and whether the daily record card was being completed. In the follow-up appointment at 31 to

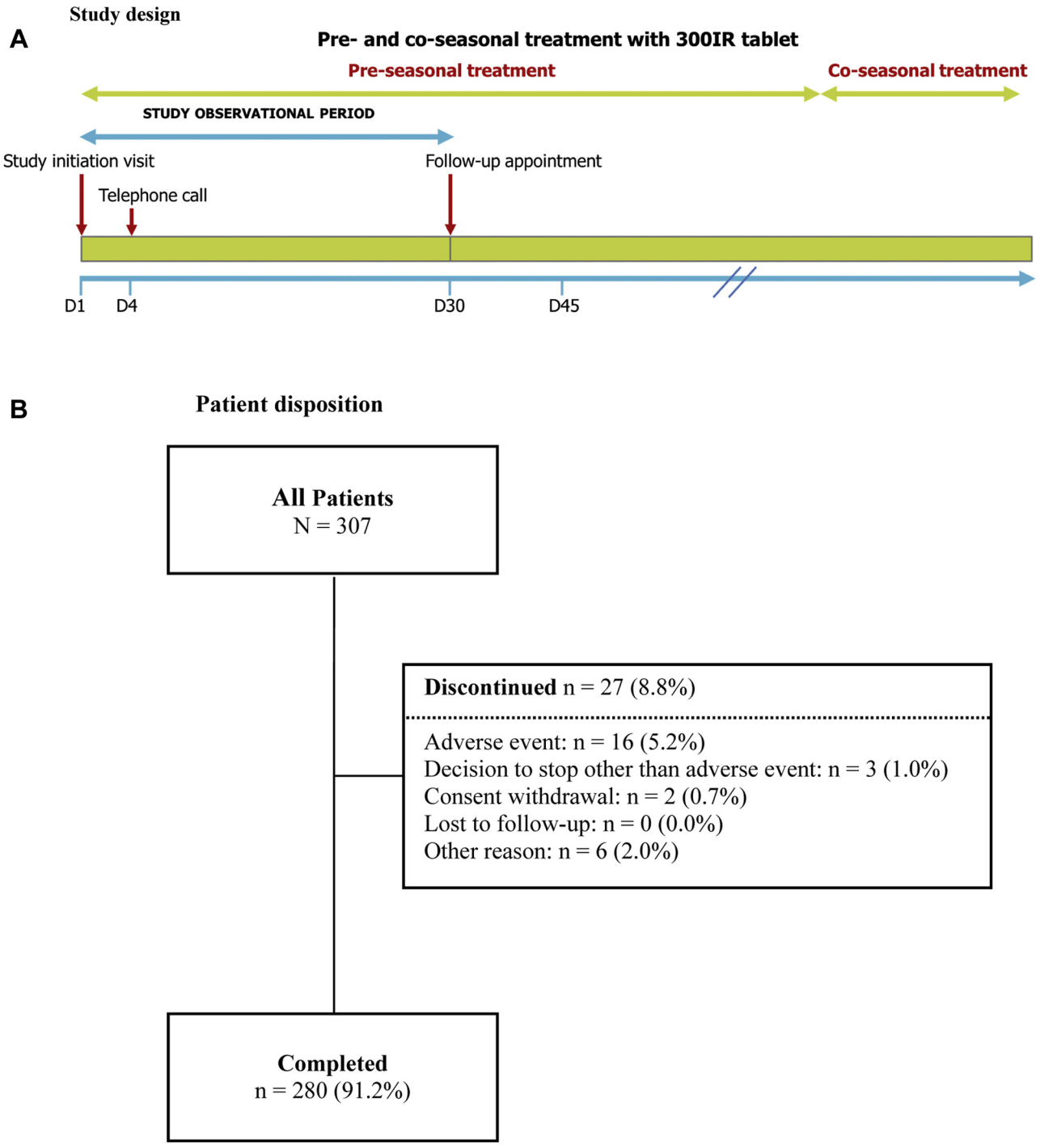

Figure 1. Study design and timeline (A) and disposition of patients (B).

45 days after the study initiation visit, the physician reviewed the daily record card with the parent/guardian.

Safety analyses included AEs that started from the day of the first administration of the medicinal product up to 30 days after this date, inclusive. Adverse events were characterized as follows: description of AE, onset day and time, duration, severity, outcome, recurrence, action taken, relationship to the drug (not related, unlikely, possible, probable/likely, highly probable/certain), and seriousness. Serious AEs were defined as any untoward medical occurrence or effect that at any dose resulted in death, was life-threatening, required hospitalization or prolongation of existing inpatients' hospitalization, resulted in persistent or significant disability or incapacity, or was otherwise considered as medically significant (ie, based upon appropriate medical judgment, any AE that might jeopardize the patient or might require medical or surgical intervention to prevent 1 of the other outcomes listed above). Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0. Adverse drug reactions (ADRs) were defined as AEs suspected by the physician to be related to the medicinal product.

Treatment compliance (%) was recorded at the follow-up appointment and was calculated as follows: 100 × (number of tablets taken/

number of tablets the patient should have taken). Based on previous reviews of adherence to allergy immunotherapy, a patient was classified as compliant if their overall compliance was 80% or greater.[35]

Statistical Analysis

The safety population for analysis included all patients who received at least 1 dose of 5-grass tablet. A sample size of 300 patients was calculated to detect an event at a 1% frequency, with a 95% probability of observing at least 1 occurrence of an event.

All analyses were carried out using Statistical Analysis System (SAS) for Windows version 9.4 (SAS Institute, Cary, NC). Descriptive statistics were used to evaluate demographic data, baseline characteristics, AEs, and ADRs. Continuous variables were reported as mean ± standard deviation; categorical variables were reported as the number of patients (percentage).

Results

Patients Enrolled

The three European countries had 63 active study centers, which enrolled a total of 307 children. All 307 patients received at least 1 dose of 5-grass tablet and constituted the safety analysis set. A total of 280 patients completed the 30-day study (Fig 1B). The primary reason for not completing the study was occurrence of AEs (16/307 [5.2%] of patients).

The baseline demographic and clinical characteristics of the patients across age classes are shown in Tables 1 and 2. Mean age was 7.1 years, and 71% of the patients were male. Before starting treatment, patients had had grass pollen–induced allergic rhinitis symptoms for approximately 2 years, and 76% had conjunctivitis symptoms.

Overall, allergy history and medical conditions related to allergy were broadly consistent across age classes (Tables 1 and 2) except for atopic dermatitis, which was more frequent among 5-year-olds than among 6-, 7-, 8-, and 9-year-olds (21% vs 8% combined average for the other 4 age classes). Polysensitization (defined as a positive reaction on skin prick test to at least 1 other allergen in addition to grass pollen—not performed for 52/307 patients) was recorded in 58% of the overall patient population, and concomitant allergic diseases among patients included house dust mite allergy (24%), food allergy (17%), allergy to animals (15%), fungal allergy (7%), and drug hypersensitivity (3%). Skin disorders including atopic dermatitis were reported in 17% of patients. At inclusion, 36% of the patients had asthma (excluding severe, unstable, or uncontrolled asthma). Fifty-nine percent of patients used concomitant medications to control their ARC or asthma symptoms or to manage AEs.

Concomitant medications included systemic antihistamines (30% of patients), inhaled adrenergic agents (14% of patients, including a corticosteroid [CS]/beta-agonist combination for 7.5% of patients), decongestants and other nasal preparations for topical use (14% of patients), inhaled CS (7.2% of patients), and systemic CS (3.6% of patients).

Inhaled CS alone or in combination were used mainly to control patients' asthma (37 patients [12%]) or to treat AEs (2 patients [0.7%] ie, 1 patient with asthma reporting worsening asthma and cough and 1 patient without asthma reporting cough).

Systemic CS were used to manage AEs (9 patients [2.9%]), including asthma (in 2 patients with asthma at inclusion), angioedema, lip edema, throat irritation, or to control other medical conditions (2 patients [0.7%]; including 1 patient with allergic asthma).

The patients' mean exposure to treatment during the study was 28.9 (±5.55) days, and treatment compliance was 96%.

Safety Findings

Adverse Events and Adverse Drug Reactions

Overall, 233 of 307 (76%) patients reported at least 1 AE (Table 3). The AEs were more frequent among 5-year-olds (41/47 [87%] vs an average of 192/260 [74%] for the other 4 age classes combined).

Over the first treatment month (ie, over the study duration), ADRs were determined by the investigator to have arisen in just over half (173/307 [56%]) of the overall population (Table 3) and were more frequent among 8-year-olds (40/61 [66%] vs an average of 133 of 246 [54%] for the other 4 age classes combined). The ADRs resolved spontaneously in 93% (161/173) of the patients with ADRs. The ADRs were mainly application-site reactions (throat irritation, oral pruritus, oral paresthesia) and of mild to moderate intensity as assessed by the investigator; ADRs were evaluated as mild in 138 of 173 (80%), moderate in 66 of 173 (38%), and severe in 10 of 173 (6%) patients with ADRs.

The percentages of patients (based on the total of 173 patients with ADRs) with first occurrence of ADRs on each day of the study are represented in Figure 2A. Within 24 hours after starting treatment, ADRs had arisen in 61 of 173 (35%) of patients with ADRs. Within 3 days of treatment, this number had increased to 114 of 173 (66%), and by 1 week of treatment 143 of 173 (83%) had reported ADRs.

The time to onset related to treatment administration (≤30 minutes or >30 minutes) is also indicated in Figure 2A, and throughout the study, ADRs most frequently occurred within 30 minutes after treatment administration. Overall, ADRs were short-lasting rather than persistent (Fig 3). More than 30% of all ADRs lasted less than 2 hours, and over half lasted less than 2 days, whereas 30% of all ADRs lasted more than 1 week. The median duration of ADRs arising within the first 24 hours of treatment was 4.7 days (range, 2 minutes to 51.3 days).

The most frequently reported ADRs (>5% of patients in the overall population) were application-site reactions (Table 3), in particular: throat irritation (68/173 [39%] of the patients with ADRs), oral pruritus (36/173 [21%]), and oral paresthesia (34/173 [20%]). Overall, the median time to onset of the most frequently reported ADRs was 3.0 days (range, 1-29 days), and median times to onset of throat irritation, oral pruritus, and oral paresthesia were 2.5, 2.0, and 2.0 days, respectively. The most frequently reported ADRs were generally short-lasting (Fig 3).

Recurrences of ADRs were identified in 26% (45/173) of the patients with ADRs. These were also most frequently application-site reactions (Table 4): throat irritation (12%), oral paresthesia (5%), and tongue pruritus (3.5%), which all tended to be short-lasting (median durations of 1 day, 2 days, and 4 hours, respectively).

Serious ADRs were reported in 2 patients. One patient with a medical history of asthma experienced oral pruritus, mild urticaria, and asthmatic attack (considered to be a grade II anaphylaxis and related to the medicinal product by the physician) on day 5, which was managed with inhaled salbutamol and oral antihistamine. The patient then continued treatment through to the end of the pollen season without any further problems. One patient was hospitalized overnight for severe lip/eye swelling (angioedema) on day 26 and recovered within 6 hours after treatment with intravenous antihistamine and CS. Both events started within 30 minutes after treatment administration. No admissions to the intensive care unit or use of epinephrine were reported.

Adverse events led to treatment discontinuation in 16 patients. These adverse events were predominantly application-site reactions (10/16 patients) and ocular events (3/16 patients).

Table 1
Baseline Demographic Characteristics and Allergy History of the Study Population by Age Classes

	Age classes					Overall
	5 years	6 years	7 years	8 years	9 years	
	N = 47 (15.3%)	N = 65 (21.2%)	N = 69 (22.5%)	N = 61 (19.9%)	N = 65 (21.2%)	N = 307 (100%)
Sex: male, n (%)	37 (78.7%)	45 (69.2%)	44 (63.8%)	43 (70.5%)	50 (76.9%)	219 (71.3%)
Age [years]						
N	—	—	—	—	—	307
Mean (SD)	—	—	—	—	—	7.1 (1.42)
Range	—	—	—	—	—	4-12[a]
Duration of grass pollen allergic rhinitis [years]						
Mean (SD)	1.46 (0.795)	2.03 (1.215)	2.39 (1.527)	2.10 (1.545)	2.51 (1.892)	2.14 (1.502)
Median	1.58	1.83	2.50	1.83	2.33	1.83
Range	0.1-2.9	0.2-5.8	0.1-6.3	0.1-7.7	0.1-7.9	0.1-7.9
Patients with conjunctivitis, n (%)	38 (80.9%)	52 (80.0%)	51 (73.9%)	46 (75.4%)	46 (70.8%)	233 (75.9%)
Patients with asthma, n (%)	17 (36.2%)	29 (44.6%)	26 (37.7%)	22 (36.1%)	17 (26.2%)	111 (36.2%)
Sensitization status, n (%)						
Monosensitized	9 (27.3%)	16 (31.4%)	11 (18.0%)	23 (42.6%)	17 (30.4%)	76 (29.8%)[b]
Polysensitized	24 (72.7%)	35 (68.6%)	50 (82.0%)	31 (57.4%)	39 (69.6%)	179 (70.2%)[b]
Missing	14	14	8	7	9	52
Cutaneous test for grass pollen, n (%)						
Positive	33 (70.2%)	52 (80.0%)	61 (88.4%)	54 (88.5%)	57 (87.7%)	257 (83.7%)
Negative	1 (2.1%)	1 (1.5%)	0	1 (1.6%)	1 (1.5%)	4 (1.3%)
Not done	13 (27.7%)	12 (18.5%)	8 (11.6%)	6 (9.8%)	7 (10.8%)	46 (15.0%)
Grass pollen specific serum IgE, n (%)						
Positive	31 (66.0%)	39 (60.0%)	42 (60.9%)	34 (55.7%)	40 (61.5%)	186 (60.6%)
Negative	2 (4.3%)	1 (1.5%)	0	1 (1.6%)	2 (3.1%)	6 (2.0%)
Not done	14 (29.8%)	25 (38.5%)	27 (39.1%)	26 (42.6%)	23 (35.4%)	115 (37.5%)

N, Number of patients treated; n, Number of patients with data; SD, standard deviation; %, percentage based on the number of patients in the corresponding column.
[a]For 1 patient, the age was calculated as 4 years because the day of birth was not collected in the case report form, but the patient was actually 5 years old. Three patients were older than 9 years and were considered as minor deviations from the protocol inclusion criteria.
[b]Sensitization status for any other allergen than grass was missing for N = 52 patients of the 307 enrolled patients. The percentages of monosensitized and polysensitized patients are calculated as follows: 24.8% = (100 × 76)/307 and 58.3% = (100 × 179)/307.

Subpopulations of patients with Asthma and Polysensitized Patients

Adverse drug reactions were reported by 56 (50%) of the 111 patients with asthma at baseline (vs 117/196 [60%] patients without asthma at baseline) and 99 (55%) of the 179 polysensitized patients (vs 46/76 [61%] monosensitized patients). The percentages of patients with asthma (based on N = 56) and polysensitized patients (based on N = 99) with first occurrence of ADRs on each day of the study are represented in Figure 2B and 2C. Within the first 24 hours after starting treatment, ADRs were reported by 21 of 56 (38%) of the subpopulation with asthma with ADRs (vs 40/117 [34%] for patients without asthma) and by 41 of 99 (41%) of the polysensitized subpopulation with ADRs (vs 16/46 [35%] for monosensitized patients). By 1 week, this had increased to 48 of 56 (86%) for the subpopulation with asthma (vs 95/117 [81%] for patients without asthma) and 83 of 99 (84%) for the polysensitized subpopulation (vs 39/46 [85%] for monosensitized patients).

The most common ADRs in the subpopulation with asthma and the polysensitized subpopulations were also application-site reactions: throat irritation, oral pruritus, and oral paresthesia (Table 3). Compared with the subpopulation without asthma and the monosensitized counterparts, no notable differences were seen in the frequency of first occurring and recurrent ADRs (Tables 3 and 4).

Adverse events leading to treatment discontinuation were predominantly application-site reactions and arose in 4 of 111 (4%) of the subpopulation with asthma (vs 12/196 [6%] of patients without asthma) and 9 of 179 (5%) polysensitized patients (vs 5/76 [7%] of monosensitized patients).

Discussion

The current study was in routine clinical settings and evaluated the safety of 5-grass tablet over the first month of treatment in 307 children aged 5 to 9 years with ARC. Adverse events were reported by 76% of patients and were suspected to be ADRs in 56% of patients. Adverse drug reactions were mainly mild to moderate transient application-site reactions, were generally short-lasting,

Table 2
Summary of Concomitant Medical Conditions Related to Allergy at Baseline

	Age classes					Overall
	5 years	6 years	7 years	8 years	9 years	
	N = 47 (15.3%)	N = 65 (21.2%)	N = 69 (22.5%)	N = 61 (19.9%)	N = 65 (21.2%)	N = 307 (100%)
Immune system disorders, n (%)	47 (100.0%)	65 (100.0%)	69 (100.0%)	61 (100.0%)	65 (100.0%)	307 (100.0%)
Seasonal allergy	47 (100.0%)	65 (100.0%)	69 (100.0%)	61 (100.0%)	65 (100.0%)	307 (100%)
House dust allergy	11 (23.4%)	15 (23.1%)	22 (31.9%)	12 (19.7%)	14 (21.5%)	74 (24.1%)
Food allergy	10 (21.3%)	8 (12.3%)	16 (23.2%)	8 (13.1%)	10 (15.4%)	52 (16.9%)
Allergy to animal	5 (10.6%)	12 (18.5%)	18 (26.1%)	6 (9.8%)	5 (7.7%)	46 (15.0%)
Mycotic allergy	2 (4.3%)	5 (7.7%)	8 (11.6%)	3 (4.9%)	2 (3.1%)	20 (6.5%)
Drug hypersensitivity	0	3 (4.6%)	5 (7.2%)	1 (1.6%)	1 (1.5%)	10 (3.3%)
Skin and subcutaneous tissue disorders, n (%)	15 (31.9%)	11 (16.9%)	10 (14.5%)	8 (13.1%)	9 (13.8%)	53 (17.3%)
Dermatitis atopic	10 (21.3%)	5 (7.7%)	6 (8.7%)	6 (9.8%)	5 (7.7%)	32 (10.4%)
Neurodermatitis	3 (6.4%)	3 (4.6%)	0	0	2 (3.1%)	8 (2.6%)
Eczema	0	2 (3.1%)	3 (4.3%)	2 (3.3%)	0	7 (2.3%)

N, number of patients treated; n, number of patients with data; %, percentage based on the number of patients in the corresponding column.

Table 3
Overview of Adverse Events and Adverse Drug Reactions

	Age classes					Asthma status		Sensitization status[a]		Overall
	5 years	6 years	7 years	8 years	9 years	With asthma	Without asthma	Polysensitized	Monosensitized	
	N = 47 (15.3%)	N = 65 (21.2%)	N = 69 (22.5%)	N = 61 (19.9%)	N = 65 (21.2%)	N = 111 (36.2%)	N = 196 (63.8%)	N = 179 (58.3%)	N = 76 (24.8%)	N = 307 (100%)
Patients reporting adverse events, n (%)	41 (87.2%)	49 (75.4%)	51 (73.9%)	46 (75.4%)	46 (70.8%)	85 (76.6%)	148 (75.5%)	129 (72.1%)	60 (78.9%)	233 (75.9%)
Patients with serious adverse events, n (%)	0	1 (1.5%)	0	1 (1.6%)	0	1 (0.9%)	1 (0.5%)	1 (0.6%)	0	2 (0.7%)
Adverse events leading to premature study withdrawal, n (%)	4 (8.5%)	4 (6.2%)	2 (2.9%)	4 (6.6%)	2 (3.1%)	4 (3.6%)	12 (6.1%)	9 (5.0%)	5 (6.6%)	16 (5.2%)
Patients reporting adverse drug reactions, n (%)	23 (48.9%)	34 (52.3%)	40 (58.0%)	40 (65.6%)	36 (55.4%)	56 (50.5%)	117 (59.7%)	99 (55.3%)	46 (60.5%)	173 (56.4%)
Severity of adverse drug reactions, n (%)										
Mild	19 (40.4%)	25 (38.5%)	33 (47.8%)	34 (55.7%)	27 (41.5%)	48 (43.2%)	90 (45.9%)	82 (45.8%)	37 (48.7%)	138 (45.0%)
Moderate	10 (21.3%)	14 (21.5%)	11 (15.9%)	14 (23.0%)	17 (26.2%)	17 (15.3%)	49 (25.0%)	37 (20.7%)	17 (22.4%)	66 (21.5%)
Severe	1 (2.1%)	2 (3.1%)	1 (1.4%)	3 (4.9 %)	3 (4.6 %)	3 (2.7%)	7 (3.6%)	5 (2.8%)	2 (2.6%)	10 (3.3%)
Most frequently reported adverse drug reactions[b] (PT), n (%)										
Throat irritation	7 (14.9%)	13 (20.0%)	17 (24.6%)	16 (26.2%)	15 (23.1%)	19 (17.1%)	49 (25.0%)	41 (22.9%)	18 (23.7%)	68 (22.1%)
Oral pruritus	1 (2.1%)	9 (13.8%)	8 (11.6%)	7 (11.5%)	11 (16.9%)	12 (10.8%)	24 (12.2%)	22 (12.3%)	10 (13.2%)	36 (11.7%)
Paresthesia oral	6 (12.8%)	4 (6.2%)	6 (8.7%)	11 (18.0%)	7 (10.8%)	11 (9.9%)	23 (11.7%)	21 (11.7%)	8 (10.5%)	34 (11.1%)
Tongue pruritus	2 (4.3%)	6 (9.2%)	6 (8.7%)	8 (13.1%)	3 (4.6%)	5 (4.5%)	20 (10.2%)	13 (7.3%)	9 (11.8%)	25 (8.1%)
Edema mouth	2 (4.3%)	1 (1.5%)	3 (4.3%)	5 (8.2%)	8 (12.3%)	3 (2.7%)	16 (8.2%)	9 (5.0%)	6 (7.9%)	19 (6.2%)
Cough	4 (8.5%)	0	5 (7.2%)	4 (6.6%)	6 (9.2%)	6 (5.4%)	13 (6.6%)	11 (6.1%)	5 (6.6%)	19 (6.2%)
Ear pruritus	2 (4.3%)	2 (3.1%)	3 (4.3%)	4 (6.6%)	5 (7.7%)	2 (1.8%)	14 (7.1%)	9 (5.0%)	6 (7.9%)	16 (5.2%)

N, number of patients treated; n, number of patients with data; %, percentage based on the number of patients in the corresponding column; PT, preferred term in MedDRA version 18.0.
One patient could have more than 1 event.
[a]In this study, sensitization status for any other allergen than grass was missing for 52 patients out of the 307 enrolled.
[b]>5% of patients in the overall population.

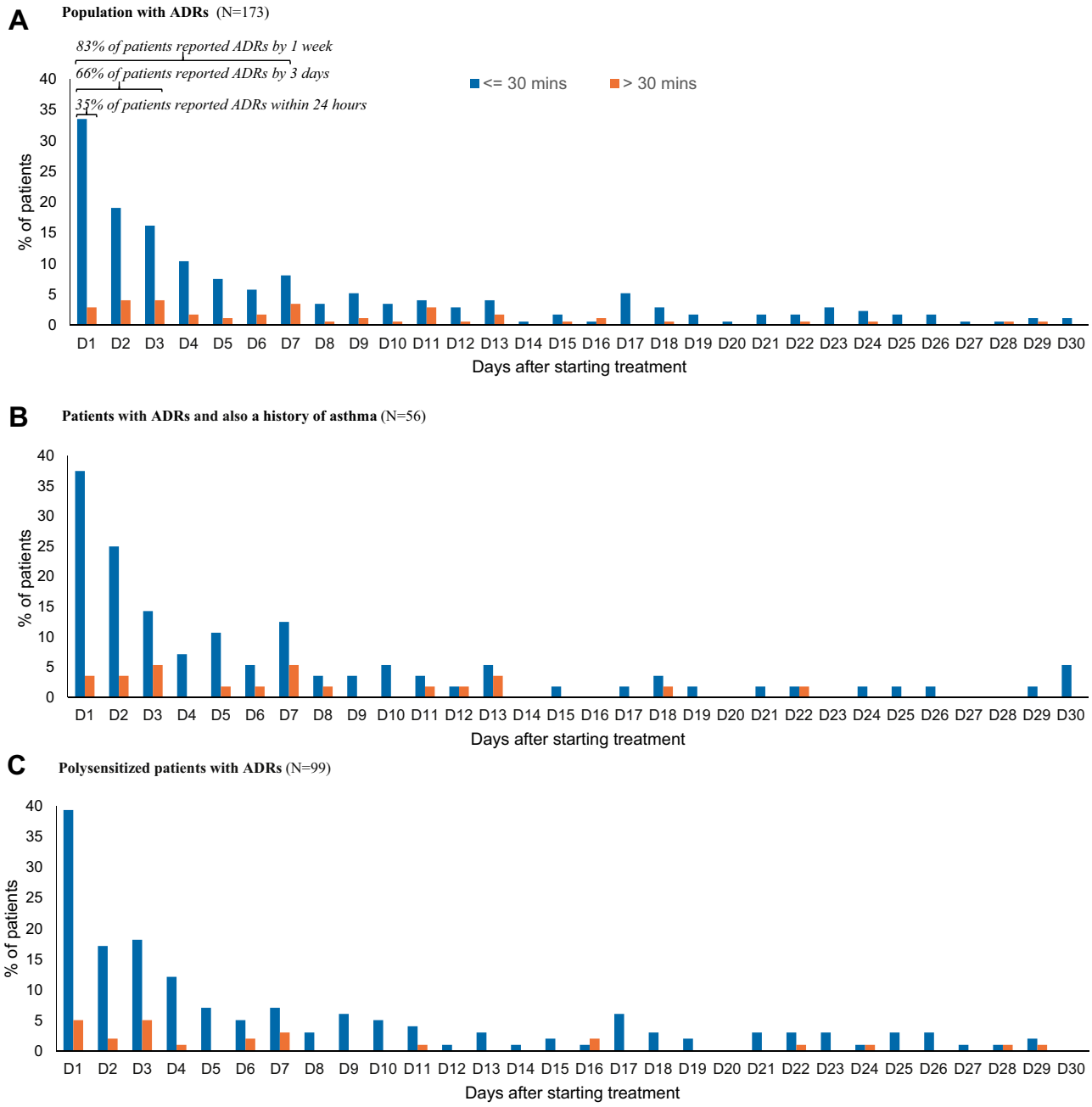

Figure 2. Percentages of patients with first occurrence of adverse drug reactions (ADRs) on each study day for the overall population with ADRs (A), patients with a history of asthma (B), and polysensitized patients (C). Percentages of patients with ADRs occurring within 30 minutes after treatment administration or longer are indicated. Note that 1 patient could have more than 1 ADR.

and tended to occur soon after treatment administration and early during treatment. The recurrent ADRs reported by a quarter of the patients with ADRs in the study were also mainly short-lasting application-site reactions. Two serious adverse reactions were reported, 1 of which did not lead to treatment discontinuation. No unexpected risks were identified, and no admission to an intensive care unit or any use of epinephrine was reported. The safety profile of 5-grass tablet was similar in patients regardless of their asthma or polysensitization status. Overall, the findings from this observational trial confirm that 5-grass tablet is safe to use in this age class of children.

Although the safety findings in our study were mostly consistent across the ages of 5 to 9 years, the number of children in each of these age groups was relatively small (47-69 patients) and any differences noted may be due to random variation. We did note a higher rate of AEs among 5-year-olds, which may be explained by respiratory tract infections being more frequent in younger children,[36] and this may partly underlie the increased frequency. Younger children also may have more attention from their caregivers, which may have impacted AE reporting in our study. We also noted a higher rate of ADRs among 8-year-olds but could not identify any underlying factor to account for this.

Current guidelines on allergy immunotherapy have highlighted the value of post-marketing observational studies performed on larger patient populations, because results from these studies will more likely reflect those seen in “real-life” clinical practice.[37] The study was conducted in a manner consistent with the recommendations outlined by the European Academy of Allergy and Clinical

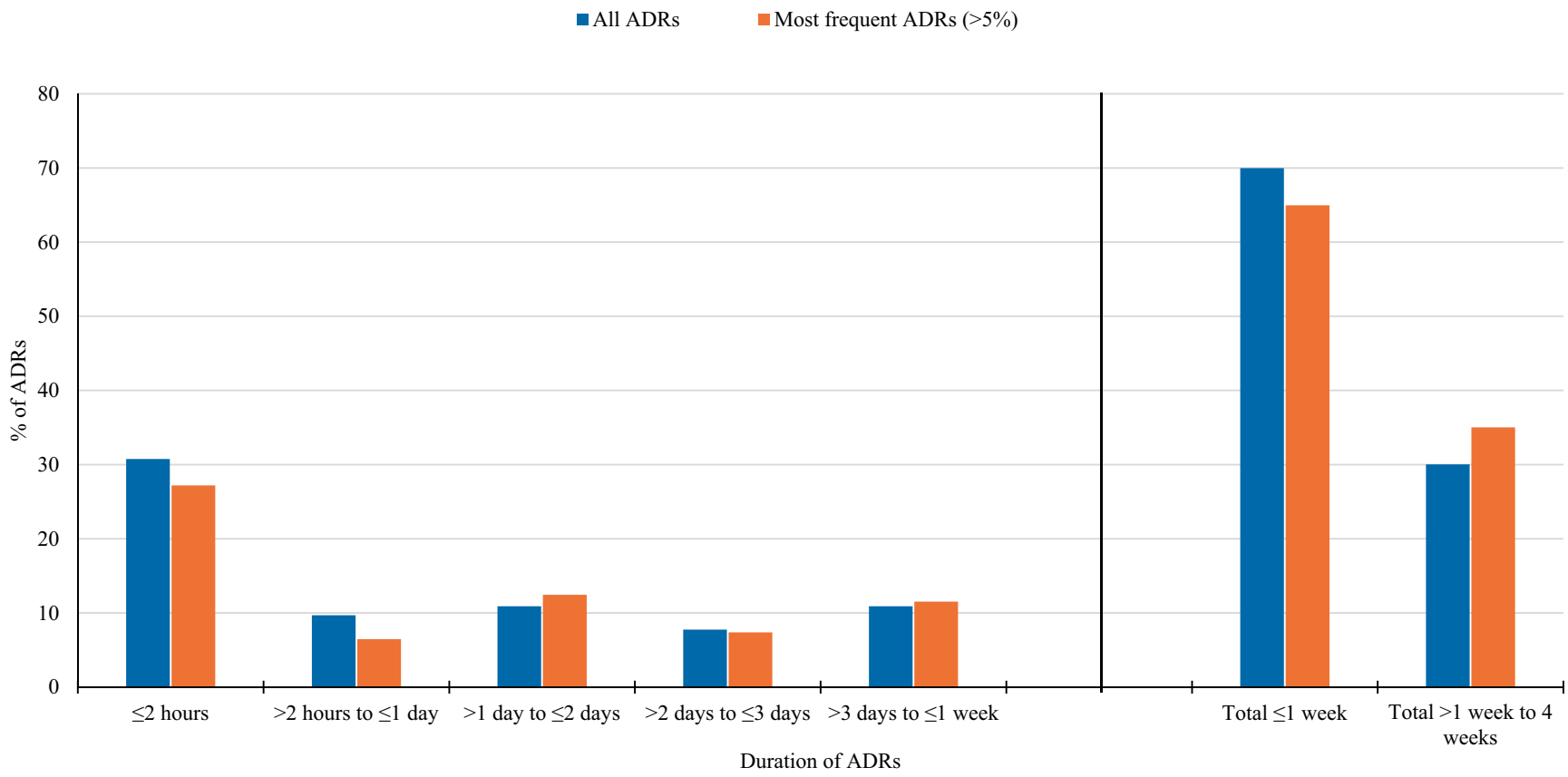

Figure 3. Duration of all adverse drug reactions (ADRs) and the most frequently reported (>5% of patients in the overall population) ADRs. Total percentages of ADRs that lasted less than 1 week, and 1 week to 4 weeks are indicated.

Table 4
Most Frequent[a] Recurrent Adverse Drug Reactions

Preferred term	Asthma status (total number of patients reporting ADRs = 173)		Sensitization status[b] (total number of patients reporting ADRs = 145)		Overall (total number of patients reporting ADRs = 173)
	With asthma (N = 56)	Without asthma (N = 117)	Polysensitized (N = 99)	Monosensitized (N = 46)	
Throat irritation n (%)	5 (8.9%)	16 (13.7%)	12 (12.1 %)	6 (13.0 %)	21 (12.1%)
Paresthesia oral n (%)	2 (3.6%)	7 (6.0%)	5 (5.1 %)	2 (4.3 %)	9 (5.2%)
Tongue pruritus n (%)	1 (1.8%)	5 (4.3%)	4 (4.0 %)	2 (4.3 %)	6 (3.5%)
Oral pruritus n (%)	2 (3.6%)	2 (1.7%)	1 (1.0 %)	2 (4.3 %)	4 (2.3%)
Edema mouth n (%)	1 (1.8%)	2 (1.7%)	1 (1.1%)	1 (2.2%)	3 (1.7%)
Cough n (%)	2 (3.6%)	1 (0.9%)	2 (2.0 %)	1 (2.2 %)	3 (1.7%)
Ear pruritus n (%)	1 (1.8%)	1 (0.9%)	2 (2.0 %)	0	2 (1.2%)

ADR, adverse drug reaction; N, number of patients with ADRs within each subpopulation; n, number of patients with data; %, percentage based on the number of patients in the corresponding column; PT, preferred term in MedDRA version 18.0.
One patient could have more than 1 event.
[a] >1% of patients in the overall population.
[b] In this study, sensitization status for any other allergen than grass was missing for 52 patients of the 307 enrolled.

Immunology for allergy immunotherapy.[38] Patients were observed under clinical supervision in an allergy clinic for 30 minutes after the first dose of 5-grass tablet, and the treatment product labeling contraindicated use in patients with uncontrolled asthma. The patients and their parent or guardian were informed on how to manage ADRs and were encouraged to ask any questions they wanted to about the study, including the treatment used. The study used detailed daily solicited reporting of events through daily record cards given to patients' parent/guardian for 1 month to monitor the occurrence of any AE as opposed to incidental reporting of events at each visit to the study investigator. This allowed the time of onset and duration of ADRs to be examined closely as well as the proportion of patients having recurrent ADRs. Such detailed characterization of ADRs has not been previously reported in clinical studies of grass-pollen immunotherapy.

A limitation of this study is that patients were evaluated only over the first month out of the 4 months of treatment prescribed before the pollen season. However, the study only evaluated safety findings, and ADRs were mainly mild, self-limiting, and occurred soon after starting treatment before decreasing markedly after 1 week, which is consistent with previous clinical safety findings.[39,40] Although even mild ADRs can lead to treatment discontinuation of grass pollen–based SLIT,[31,41] treatment was well tolerated in this study, with a compliance rate of 96%. It therefore can be argued that extending the period of evaluation would have been unlikely to yield further insights into ADRs associated with the use of 5-grass tablet among the child population. In this observational study, another limitation is that the full details regarding why patients were taking other medications in addition to 5-grass tablet are not available. Thirty percent of the patients were using oral antihistamines to control their ARC symptoms, manage AEs, treat underlying illness, or prevent occurrence of AEs. However, the terminology used by the reporting physicians was not consistent, thus preventing a precise breakdown of the reasons why antihistamines were used in the study population. A future investigation into whether patients using antihistamines together with grass pollen SLIT are less susceptible to AEs and ADRs would be of interest.

Our findings are very similar to those from a placebo-controlled study of children (aged 5-11 years) and adolescent (aged 12-17 years) ARC patients who were treated with 5-grass tablet over 4 months before and during the pollen season.[33,42] Of the 139 patients receiving 5-grass tablet, 85% presented with AEs that were mainly mild to moderate application-site reactions (oral pruritus, mouth edema, and throat irritation). Adverse drug reactions were reported in 47% of the 87 children aged 5 to 11 years.[42] Placebo-controlled trials of a timothy-grass pollen sublingual tablet in children aged 5 to 12 years with ARC have also reported similar frequencies of AEs and ADRs. In a small trial, 82% of 45 children who were administered a timothy grass pollen tablet reported AEs, and 78% reported ADRs (mainly application-site reactions),[43] whereas in a larger 5-year trial 95% of 398 children reported AEs and 61% reported ADRs.[44]

Other large observational studies have been performed on adults, adolescents, and children (including children ages 5-11 years) with ARC being administered 5-grass tablet[45–48] or timothy-grass tablet.[49,50] These studies ranged from 3 months to 2 years in duration, and all reported that grass-pollen allergy immunotherapy was very well tolerated with ADRs being mostly mild to moderate application-site reactions such as oral paresthesia, oral pruritus, throat irritation, and mouth edema. The ADRs reported in these trials arose soon after treatment administration, and the most common ADRs had median lag times of 3.5 to 5 minutes and duration of 16 minutes.[45,46] Furthermore, 43% to 72% of the populations with ADRs reported their ADRs after the first intake of treatment, and in a 2-year observational trial, 93% of ADRs arose within the first treatment year.[47] However, the rates of ADRs reported were comparatively low, ranging from 15% to 37% in child and adolescent subpopulations[45,47,48,50] to 22% to 35% in adult populations.[45,46,48] This may be because ADRs were evaluated using incidental reporting of events at each visit to the study investigator. These visits could have occurred just once during the year after the start of study treatment.[45] In contrast, the current study used solicitated reporting of events to evaluate ADR frequency. Furthermore, only immunotherapy-naïve patients were recruited into the current study, whereas the other observational studies also included patients who had previously received immunotherapies, and 1 of the studies included patients who were receiving concomitant immunotherapies for other allergic diseases.[49]

This study included a subpopulation of 111 patients with mild to moderate asthma. To our knowledge, this represents the largest studied subpopulation of patients aged 5 to 9 years with mild to moderate asthma administered 5-grass tablet. A subpopulation of 158 children with asthma aged 5 to 11 years was described in an observational study of 5-grass tablet,[45] but the authors did not report any specific safety findings for this subpopulation. In another observational study of 5-grass tablet,[47] 93 children with asthma of the same age were followed up over 2 years and reported similar percentages of ADRs compared with the children without asthma in the study. Similarly, the children with asthma treated with 5-grass tablet in the current study showed no notable differences in time of onset or frequency of ADRs compared with the children without asthma.

In conclusion, the safety findings for 5-grass tablet in this large observational trial in children aged 5 to 9 years with ARC were

consistent with those established for older patients, with no notable differences observed in the largest studied subpopulation of children with mild-to-moderate asthma. These findings further confirm the safety of this treatment in this age class, and 5-grass pollen tablet has had marketing approval since 2008 for the management of ARC in patients aged 5 to 65 years in an increasing number of countries worldwide. In the United States, marketing approval of 5-grass tablet was extended for use in patients aged 5 to 65 years in November 2018.

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