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ORIGINAL RESEARCH



Grass pollen sublingual immunotherapy tablets provide long-term relief of grass pollen-associated allergic rhinitis and reduce the risk of asthma: findings from a retrospective, real-world database subanalysis

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ABSTRACT

Background: We assessed real-world, long-term effectiveness of two marketed sublingual immunotherapy (SLIT) tablets for allergic rhinitis (AR), and their impact on allergic asthma (AA) onset/progression.

Methods: Retrospective, longitudinal German prescription database subanalysis of AR patients receiving 5- or 1-grass pollen SLIT tablets ($n = 1,466/1,385$), versus patients not using allergy immunotherapy (AIT) ($n = 71,275$).

Primary endpoint: change over time in AR symptomatic medication prescriptions after treatment cessation; secondary endpoints: new asthma onset, and change over time in asthma medication prescriptions during treatment/follow-up periods.

Results: Mean number of AR medication prescriptions was significantly decreased during follow-up (of up to 6 years) with both SLIT tablets versus the non-AIT group ($p < 0.001$).

Over the full-analysis period, proportions of patients with new-onset asthma were 8.8% (odds ratio: 0.676, $p = 0.011$), 10.3% (odds ratio: 0.720, $p = 0.060$) and 11.6% in the 5- and 1-grass pollen SLIT tablet and non-AIT groups, respectively.

For all treatment-analysis periods, both SLIT tablet groups were associated with fewer asthma medication prescriptions versus non-AIT controls.

Conclusions: These findings confirm the real-world benefits of 5- and 1-grass-pollen SLIT tablets in slower AR progression, reduced risk of new asthma onset in the non-asthmatic population, and slower asthma progression in the asthmatic population.

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Allergic rhinitis; asthma; grass pollen; real-world; sublingual immunotherapy

1. Introduction

Allergic rhinitis (AR) is a widespread chronic inflammatory condition, with sufferers experiencing considerable discomfort due to rhinorrhea, nasal congestion, sneezing, nasal and ocular pruritis, and watery eyes [1]. Globally, AR affects around half a billion people [2], and grass pollen is currently regarded as the main cause of pollen allergy worldwide giving rise to AR, allergic conjunctivitis, and asthma [3].

AR symptoms can negatively affect day-to-day and social functioning, quality of life (QoL), and mood, and cause decreased attendance, productivity, and performance at work and school [4–10]. AR is also associated with comorbidities, including allergic conjunctivitis and asthma [5,10–12]. The close association between AR and asthma is reflected in the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, which recommend mandatory testing for asthma in children with persistent AR, and vice versa [5]. AR is a frequent precursor of asthma and may be considered an independent risk factor for it [5,13].

Treatment with medications such as antihistamines or corticosteroids is often necessary to manage AR symptoms, because allergen avoidance is usually not possible, particularly in cases of grass-pollen-associated AR. However, despite the use of optimal pharmacotherapy, many patients with AR do not achieve complete relief from symptoms or long-term control. While such medications can temporarily help to reduce the incidence and severity of AR symptoms, they cannot modify the course of disease nor cure it [5].

In contrast, allergy immunotherapy (AIT) in the form of subcutaneous or sublingual immunotherapy (SCIT and SLIT, respectively) is the only disease-modifying intervention available for AR with demonstrated long-term efficacy [14,15]. AIT also appears to prevent the development of new allergen sensitizations and reduces the risk of subsequent asthma in patients with AR by inducing allergen-specific immune tolerance [15].

AIT achieves this through multiple mechanisms, including regulating T- and B-cell responses, changing antibody isotypes, and decreasing mediator release and migration of eosinophils, basophils, and mast cells to affected tissues, with a

pivotal role being played by allergen-specific T-regulatory cells in the down-regulation of the Th2 response [16].

In patients with moderate-to-severe AR, grass pollen SLIT tablets have demonstrated sustained clinical benefits in symptom control, need for rescue medication use and QoL over 3 years of treatment [17,18], and a long-term effect for at least 2 years after treatment cessation [19,20]. In patients with mild-to-moderate AA, there is evidence that AIT can provide symptomatic relief and reduce medication use [21–23].

Two SLIT tablets are currently licensed in the European Union and the United States for the treatment of grass-pollen-associated AR: the 5-grass-pollen SLIT tablet (Oralair®; Stallergenes Greer, Antony, France) and the 1-grass-pollen SLIT tablet (Grazax™/Grastek®; ALK-Abelló, Hørsholm, Denmark/Merck, Kenilworth, NJ, USA). The 5- and 1-grass-pollen SLIT tablets have been marketed in Germany since 2008 and 2006, respectively.

There is an increasing need to demonstrate long-term efficacy and preventive effects for therapies in a real-world setting, with bodies such as the US FDA and the UK National Institute for Health and Care Excellence now recognizing the value of real-world evidence in regulatory decision-making [24,25]. However, there remains a paucity of clinical trial evidence for the efficacy of AIT beyond 2 years post-treatment and for its long-term preventive effects on asthma and new sensitizations [26]. Real-world evidence can aid informed treatment decisions by providing data that take into account variables such as the patient population, demographics, and comorbidities [25,27–29]. Similarly, data from real-world studies on the progression of AR and/or asthma in patients receiving AIT are sparse.

A recent retrospective, real-world database analysis evaluated the effect of grass pollen SLIT tablets in addition to AR treatment on the progression of AR, occurrence of asthma (in patients without this condition at baseline), and the progression of asthma (in patients with this condition at baseline), compared with symptomatic AR treatment without AIT [28]. Following on from this primary report, we present findings from a subanalysis, which was performed to assess the real-world, long-term efficacy of the licensed 5- and 1-grass-pollen SLIT tablets for AR and their impact on asthma onset and progression.

2. Methods

2.1. Overall study design

The study design and methodology have been reported previously [28] and are described briefly here. In this retrospective analysis of data extracted from a German longitudinal prescription database (LRx, IMS Health, Frankfurt am Main, Germany) [30], patients with AR treated with 5- or 1-grass-pollen SLIT tablets were compared with a control group not receiving AIT, who had received symptomatic AR medications only. Patient profiles (e.g. the presence and/or progression of grass-pollen-induced AR and/or asthma) were inferred from proxy prescription data. The overall analysis period ran from January 2009 to February 2016.

2.2. Data sets and proxy clinical data

The LRx database contains information on approximately 60% of all prescriptions reimbursed by statutory health insurance funds in Germany [30], but over-the-counter (OTC) medications were not recorded. In line with German legislation on anonymized database analyses, informed consent was not required. The prescription of nasal corticosteroids at least once over the grass pollen season for 3 consecutive years was used to identify control (non-AIT) patients with AR. Overall symptomatic medication use was tracked and scored to assess AR progression in the selected patients. Only AR medication prescriptions occurring 1 month before and during the grass pollen season in Germany (May–August) were analyzed [31].

Similarly, the occurrence and progression of asthma were estimated from prescriptions of guideline-recommended medications [32]. Asthma progression was estimated by tracking prescriptions for long-acting beta-agonists (LABAs), combinations of LABAs and inhaled corticosteroids (ICSs), methylxanthines, leukotriene antagonists and depot formulations of systemic corticosteroids, as well as short-acting beta-agonists (SABAs) and ICSs. Depot formulations of systemic corticosteroids are not a recommended treatment option for asthma, but are sometimes used; therefore, a sensitivity analysis was also performed after excluding them, which showed no impact on the results.

2.3. Analytical time periods

The index date was defined as the date of first SLIT tablet prescription (for the SLIT tablet groups) or the date of second intranasal corticosteroid (INS) prescription (for the non-AIT control group; patients included in this group were requested to have a prescription of this drug class at least once over the grass pollen season for 3 consecutive years, with the first year before index as the pre-index period and the 2 subsequent years representing the treatment period). The pre-index period was defined as the 365-day period before the index date. The on-treatment period extended from the index date to the expiry date of last SLIT tablet prescription (SLIT tablet groups) or the last AR medication prescription in a subsequent pollen season (non-AIT group). The follow-up period extended from the end of the on-treatment period to study end (data lock February 2016), and the full-analysis period combined the on-treatment and follow-up periods.

2.4. Study population

Patients in the SLIT tablet groups were selected on the basis of a SLIT tablet prescription in ≥ 2 successive treatment cycles. Patients with an index date from 2009–2012 were included, thus ensuring that the patient was observable for at least 365 days prior to this date since the database was created in January 2008. Patients in the non-AIT group were selected on the basis of ≥ 1 INS prescription during the grass pollen season or in the month before the grass pollen season (with the first year being 2008, 2009, 2010, or 2011) (Figure 2). Inclusion and

exclusion criteria for both groups have been described previously [28].

In order to avoid confounding bias due to differences in length and intensity of the grass pollen season in different years, patients in the SLIT tablet groups and the non-AIT group were matched by index year. The process was repeated until no eligible non-AIT patients remained (final matching ratio: 25:1). Possible confounders, other than index year, were subsequently corrected for in all analyses by multiple regressions. Covariates included age, gender, prescribing physician specialty, presence of asthma prior to index date, and number of years on SLIT.

2.5. Study endpoints

The primary endpoint was the change over time in prescriptions of AR symptomatic medications after treatment cessation. The secondary endpoints were new asthma onset, defined as the time to the first prescription of SABAs or ICSS, during treatment and after treatment cessation (as a binary (yes/no) variable) in patients without asthma at the index date, and the change over time in asthma medication prescriptions during the on-treatment and follow-up periods in patients with asthma at the index date. The progressions of AR and asthma were analyzed using linear regression. In secondary analyses, time to new asthma onset was assessed in a Cox proportional hazard regression. Interactions between independent variables were not included in the regression.

AR progression was only analyzed for the follow-up period because the structure of the selection process in the control group (prescription of INS for the two subsequent years of the on-treatment period) distorted this variable during the on-treatment period. In contrast, the asthma analyses were performed for the on-treatment, follow-up, and full-analysis periods.

All analyses were carried out using SAS software (version 9.3, SAS Institute, Inc., Cary, NC, USA). The threshold for statistical significance was set to $p < 0.05$ in all cases.

3. Results

3.1. Characteristics of the study population

As described previously, the IMS LRx database contained 105,069 patients with AR and ≥ 1 prescription of SLIT tablets (5-grass-pollen SLIT tablets: $n = 51,268$; 1-grass-pollen SLIT tablets: $n = 53,801$), and 15,552,229 patients with AR who received symptomatic treatment only [28]. After applying inclusion and exclusion criteria, 1466 patients who received 5-grass-pollen SLIT tablets, 1385 patients who received 1-grass-pollen SLIT tablets, and 71,275 control non-AIT patients were selected for analysis (Table 1).

The proportion of asthma-free patients, and the gender distribution, at index date was similar between all three patient groups (Table 1). For patients receiving either SLIT tablet formulation, age distribution at index date was comparable, but in the non-AIT group, there were markedly fewer patients aged < 18 years (Table 1). The age structure of the non-AIT group is in keeping with that of the general population of patients with AR in Germany, who are largely aged > 40 years.

Reflecting the age distribution, the proportion of patients who were prescribed treatment by a pediatrician was 10-fold lower in the non-AIT group than the SLIT tablet groups. A greater proportion of patients in the SLIT tablet groups were prescribed treatment by dermatologists, compared with the non-AIT group, and general practitioners were the most-common type of prescribing physician for patients in the non-AIT group (Table 1).

Table 1. Demographic and prescription-related characteristics of patients with AR at the index date or during the pre-index period.

Parameter	5-grass-pollen SLIT tablet group $n = 1,466$		1-grass-pollen SLIT tablet group $n = 1,385$		Non-AIT group $n = 71,275$	
Gender, n (%)						
• Male	536	(36.6)	534	(38.6)	25,286	(35.5)
• Female	498	(34.0)	486	(35.1)	26,585	(37.3)
• Unknown	432	(29.5)	365	(26.4)	19,404	(27.2)
Age, n (%)						
• 5–17 years	720	(49.1)	666	(48.1)	5,327	(7.5)
• ≥ 18 years	746	(50.9)	719	(51.9)	65,948	(92.5)
Main prescriber, n (%)						
• ENT specialist	534	(36.4)	554	(40.0)	26,109	(36.6)
• Dermatologist	256	(17.5)	266	(19.2)	946	(1.3)
• Pulmonologist	81	(5.5)	116	(8.4)	1,371	(1.9)
• Pediatrician	330	(22.5)	301	(21.7)	1,528	(2.1)
• Internal medicine specialist	32	(2.2)	35	(2.5)	9,150	(12.8)
• General practitioner	213	(14.5)	92	(6.6)	31,370	(44.0)
• Other specialty	20	(1.4)	21	(1.5)	801	(1.1)
Asthma status, n (%)						
• No asthma	1,138	(77.6)	1,053	(76.0)	53,718	(75.4)
• With asthma	304	(20.7)	300	(21.7)	14,954	(21.0)
• History of prior asthma (absent for > 1 year before index date)	24	(1.6)	32	(2.3)	2,603	(3.7)
AR medication prescriptions per patient per year in the pre-index period, mean $\pm$ SD (range) [n]	1.93 $\pm$ 1.51 (1–15) [1,466]		2.09 $\pm$ 1.84 (1–19) [1,385]		3.65 $\pm$ 2.83 (1–73) [71,275]	
Asthma medication prescriptions per patient per year in the pre-index period, mean $\pm$ SD (range) [n]	3.36 $\pm$ 2.58 (1–16) [304]		3.40 $\pm$ 2.87 (1–28) [300]		3.00 $\pm$ 2.30 (1–40) [14,954]	

AIT, allergy immunotherapy; AR, allergic rhinitis; ENT, ear, nose and throat; SD, standard deviation; SLIT, sublingual immunotherapy.

3.2. SLIT treatment patterns

SLIT was administered for ≥ 3 years in 59% and 70% of patients with AR receiving 5- and 1-grass-pollen SLIT tablets, respectively, in line with the recommended treatment duration of 3 grass pollen seasons.

3.3. Progression of AR after treatment cessation

After treatment cessation and for up to 6 years, the mean number of AR medication prescriptions was lower for all patient groups, compared with the pre-index period. The relative decrease in mean ($\pm$ SD) AR medication prescriptions per year was greatest in the 5-pollen SLIT tablet group (from 1.93 ± 1.51 to 0.19 ± 0.57 , equating to a > 10 -fold decrease), followed by the 1-pollen SLIT tablet group (from 2.09 ± 1.84 to 0.26 ± 0.77 , equating to an 8-fold decrease) and the non-AIT group (from 3.65 ± 2.83 to 1.10 ± 1.82 , equating to a 3-fold decrease). After adjustment for covariates, linear regression analysis of the change in AR medication prescriptions confirmed that the decrease seen at the follow-up period was significantly greater in both SLIT tablet groups, compared with the non-AIT group (regression coefficient [95% confidence interval (CI)] of -0.202 (95% CI: $-0.245, -0.158$) and -0.164 (95% CI: $-0.214, -0.114$) for the 5- and 1-grass-pollen SLIT tablet groups, respectively; both $p < 0.001$) (Figure 1).

3.4. New asthma onset

In the full-analysis period, the lowest proportion of patients who were initially free from asthma and subsequently developed it was seen in the 5-grass-pollen SLIT tablet group (8.8%, $n = 100$), compared with 10.3% ($n = 108$) and 11.6% ($n = 6,222$) of patients in the 1-grass-pollen SLIT tablet and non-AIT groups, respectively. After adjustment for covariates, treatment with the 5-grass-pollen SLIT tablet was associated with a lower risk of asthma occurrence in all analysis periods, but this only reached significance for the on-treatment and full-analysis time periods,

with a relative risk reduction of $\sim 30\%$ during both of these (Figure 2). The odds ratios for asthma occurrence versus the non-AIT group were 0.685 (95% CI: 0.484, 0.969) ($p = 0.033$), 0.565 (95% CI: 0.319, 1.002) ($p = 0.051$), and 0.676 (95% CI: 0.499, 0.915) ($p = 0.011$) for the on-treatment, follow-up, and full-analysis time periods, respectively. The 1-grass-pollen SLIT tablet was associated with a consistent trend toward the prevention of asthma in patients not suffering from it pre-index, but this failed to reach significance for all three analytical time periods (Figure 2). The odds ratios for asthma occurrence versus the non-AIT group were 0.725 (95% CI: 0.490, 1.075) ($p = 0.110$), 0.605 (95% CI: 0.315, 1.161) ($p = 0.131$), and 0.720 (95% CI: 0.511, 1.014) ($p = 0.060$) for the on-treatment, follow-up, and full-analysis time periods, respectively.

3.5. Progression of asthma

The mean number of asthma medication prescriptions was slightly higher in both SLIT tablet groups than in the non-AIT group, among patients with asthma during the pre-index period (Table 1). Throughout all treatment analysis periods, the effect of 5-grass-pollen SLIT tablet treatment was positive, but with borderline significance. The biggest reduction in asthma medication prescriptions with the 5-grass-pollen SLIT tablet occurred during the on-treatment period [mean ($\pm$ SD) prescriptions per patient: 2.77 ± 3.40 per year, equating to a 24.6% decrease], and linear regression analysis after adjustment of covariates confirmed that this was the only time period for which the effect was significant, compared with the non-AIT group ($p = 0.013$) (Figure 3). Similarly, for all three treatment analysis periods, the 1-grass-pollen SLIT tablet was associated with fewer asthma medication prescriptions, compared with the non-AIT group, but this effect was only significant for the follow-up period [mean ($\pm$ SD) prescriptions per patient: 0.70 ± 1.64 per year, equating to a 16.8% decrease; $p = 0.040$] (Figure 3). For the full-analysis time period, mean ($\pm$ SD) numbers of asthma medication prescriptions

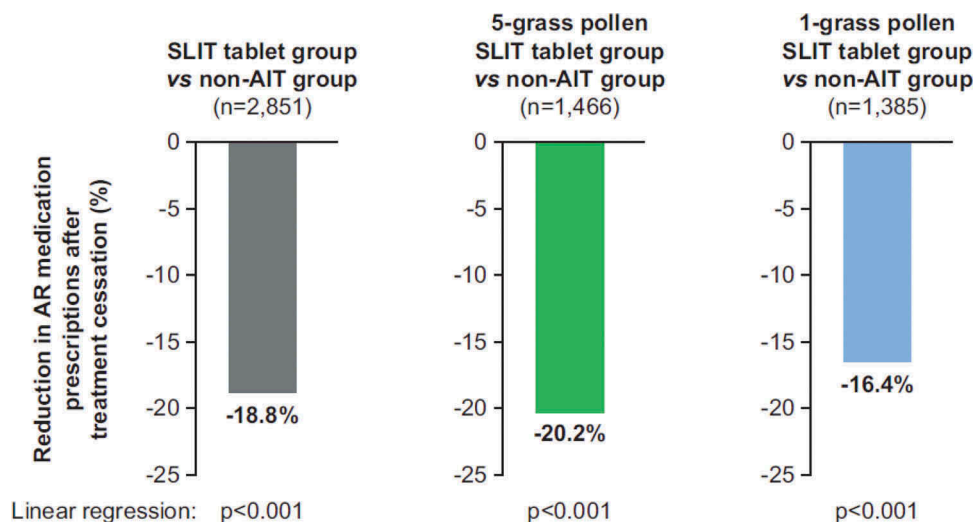


Figure 1. Linear regression analysis of change from pre-index period in AR symptomatic medication use following treatment cessation [for the SLIT tablet group and the 5- and 1-grass pollen SLIT tablet groups, compared with the non-AIT group ($n = 71,275$)].

AIT, allergy immunotherapy; AR, allergic rhinitis; SLIT, sublingual immunotherapy.

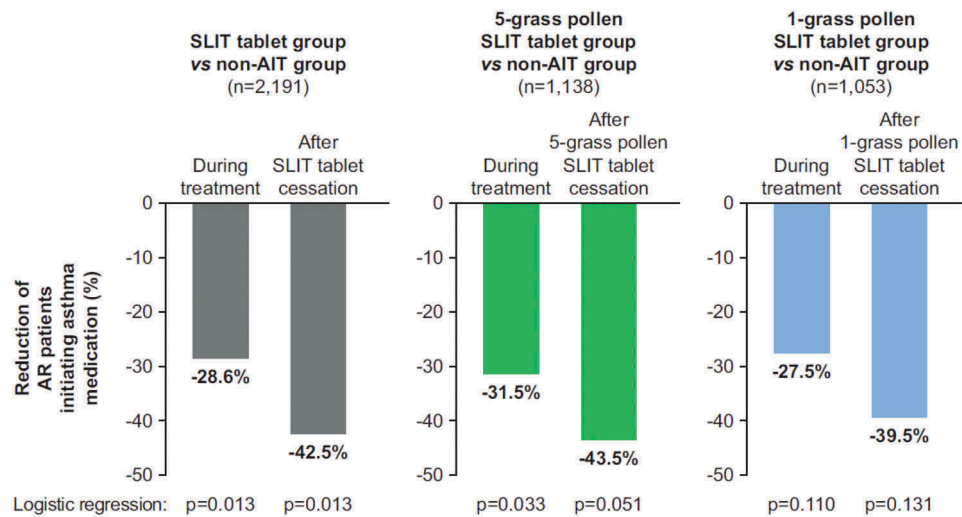


Figure 2. Logistic regression analysis of change from pre-index period in occurrence of asthma in the non-asthmatic population, measured as 2 successive prescriptions of SABAs or ICSs, on-treatment, following treatment cessation [for the SLIT tablet group, and the 5- and 1-grass pollen SLIT tablet groups, compared with the non-AIT group (n = 53,718)].

AIT, allergy immunotherapy; AR, allergic rhinitis; ICS, inhaled corticosteroid; SABA, short-acting beta-agonist; SLIT, sublingual immunotherapy.

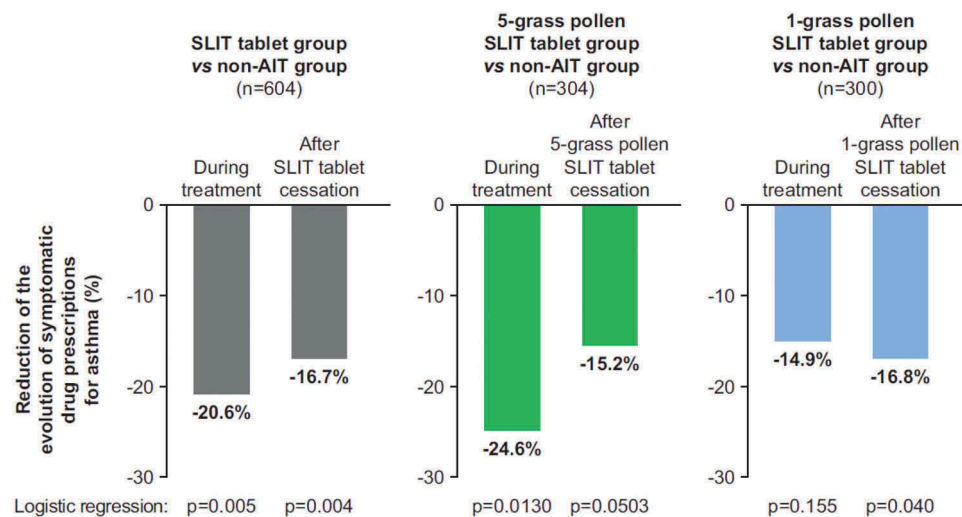


Figure 3. Linear regression analysis of change from pre-index period in asthma medication use, on-treatment, following treatment cessation [for the SLIT tablet group, and the 5- and 1-grass pollen SLIT tablet groups, compared with the non-AIT group (n = 14,954)].

AIT, allergy immunotherapy; SLIT, sublingual immunotherapy.

per patient per year were $1.38 + 1.93$ (5-grass-pollen SLIT tablet group), $1.56 + 1.95$ (1-grass-pollen SLIT tablet group), and $1.55 + 2.10$ (non-AIT group).

4. Discussion

Increasingly, regulatory and reimbursement authorities are requesting evidence of real-world effectiveness of licensed medications to confirm the efficacy seen in randomized controlled trials. The value and potential of real-world studies versus randomized controlled trials lies in moving decisions away from extrapolations based on a strictly defined population (which may only represent a small proportion of patients in daily clinical practice), to assessing whether an intervention reflects the efficacy seen in randomized controlled trials, when

used in routine circumstances [33]. Real-world studies are typically of larger scale with a longer follow-up period, compared with randomized controlled trials, and their patient populations have higher generalizability than those in randomized controlled trials [33]. The longer duration of real-world studies permits a more appropriate assessment of the long-term effects of the intervention and its safety by following the natural course of a disease (although for the present study, no safety data were collected) [33]. In addition, the characteristics of real-world studies enable evaluation of complex therapies and policies for prescribing and management, and gathering of data on treatment modalities that may not be possible in randomized controlled trials due to logistical and/or ethical constraints, thus allowing more reliable assessment of outcomes such as hospitalization, mortality, and cost-

effectiveness [33]. The present retrospective analysis of data extracted from a longitudinal prescription database since 2008 enabled follow-up of patients with AR, providing assessment of the long-term effectiveness of both grass pollen SLIT tablets marketed in Germany and their preventive effect on AR worsening and asthma prevention, for which data had previously been limited. According to the most-recent European Academy of Allergy and Clinical Immunology (EAACI) guidelines on AIT for allergy prevention [34], the up to 6 years of follow-up after stopping treatment in the present study classifies it as a long-term study (defined as ≥ 2 years of follow-up).

In the primary report analyzing SLIT use among patients in the LRx database, treatment with grass pollen SLIT tablets was associated with a clinically meaningful and significant potential reduction in AR progression of 18.8% and decreases in asthma occurrence and progression of 42.5% and 16.7%, respectively, after treatment cessation [28]. The present sub-analysis confirms the significant benefit of either 5- or 1-grass-pollen SLIT tablet use on reduction in AR progression that was observed in the primary study [28] and in randomized controlled trials [17–20]. No direct comparison was conducted between the two products; however, compared to the non-AIT group, the 5-grass-pollen SLIT tablet produced a somewhat greater reduction of the evolution of symptomatic drug prescriptions for AR than the 1-grass-pollen tablet for all treatment analysis periods and up to 6 years after SLIT treatment cessation.

The benefits of grass pollen SLIT tablets on new asthma occurrence were less robust than those for AR progression. There was a lower probability of developing asthma in the 5-grass-pollen SLIT tablet group (8.8%) versus the 1-grass-pollen SLIT tablet group (10.3%), but significance was only achieved for the on-treatment and full-analysis time periods with the 5-grass-pollen SLIT tablet. Nevertheless, the findings from all analytical time periods are consistent with each other and support the findings from the primary LRx database analysis [28] and from pediatric clinical studies [35,36], demonstrating that SLIT is associated with a significant preventative effect on the development of new-onset asthma in patients with AR, compared with standard AR pharmacotherapy.

In the primary report, there was a statistically significant benefit of SLIT on asthma progression in all three analytical time periods [28]. In the present analysis, significant reductions in asthma medication prescriptions were only seen during the on-treatment period for the 5-grass-pollen SLIT tablet and the follow-up period for the 1-grass-pollen SLIT tablet. This likely again reflects a lack of statistical power, particularly because patient numbers in the asthma comparisons were further reduced from those in the AR comparisons by the necessity to split the study population into two groups (with or without asthma pre-index). Nevertheless, it is striking that all the effect means recorded for either of the two SLIT products alone are very close to their counterparts for the main SLIT group, and it is very likely that, given higher patient numbers, significance would be reached for all treatment analysis time periods.

SLIT is primarily given to treat AR, and any positive effects on asthma prevention or progression might be considered of secondary benefit. The results therefore, to a certain extent,

reflect those of the GAP trial (a large, double-blind, placebo-controlled, randomized trial in 812 children aged 5–12 years with grass-pollen-associated allergy), which showed that 1-grass-pollen SLIT tablet treatment failed to prevent asthma using a restrictive definition of asthma based on demonstration of reversibility, but was associated with a relative reduction versus placebo in the proportion of children experiencing asthma symptoms or using asthma medication up to 2 years after treatment cessation [37].

The grass pollen SLIT tablet formulations analyzed here differ in their allergen formulation and recommended administration regimen: the 5-grass-pollen SLIT tablet contains an extract of pollens from five grass species that better mimics the IgE epitope repertoire of pollen from the most common grasses [38,39], whereas the 1-grass-pollen SLIT tablet contains timothy grass pollen extract recognizing Timothy grass-epitope only. The recommended administration scheme for the former is a unique pre- and co-seasonal regimen (starting 4 months before the expected onset of grass pollen season until season end) for three consecutive grass pollen seasons, while the latter should be administered continuously for 3 consecutive years. In real-life use, a proportion of patients in the SLIT tablet groups did not remain on-treatment for the recommended duration.

This study had a number of strengths deriving from its foundation on real-world data [28]. The patient populations in real-world data analyses, such as the large, nationwide study cohort in the present study, are more representative than those in randomized controlled trials, allowing better generalizability of the findings [33]. The longer duration of follow-up with this real-world study versus a randomized controlled trial enabled assessment of clinically relevant endpoints and the long-term benefits of SLIT tablets, compared to the standard of care. The findings also accurately reflect current clinical practice and the use of SLIT tablets for the management of AR in Germany, ensuring the high external validity of the study. In Germany, at variance to many other European countries, most cases of grass-pollen-associated allergy are managed by general practitioners and not specialists in allergy (in contrast to, e.g., house dust mite-associated allergy, which is primarily managed by allergists) [40], and this is mirrored in the main prescriber findings for the non-AIT group.

However, there are also some limitations inherent to the study [28]. The LRx prescription database does not contain specific clinical information, such as diagnostic methodology, meaning that Anatomical Therapeutic Chemical (ATC) drug class codes had to be used as proxies for the diagnosis and treatment of AR and AA. However, the choice of INs, which are specific to the treatment of AR, minimized the risk of including patients who did not have AR. Some patients in the non-AIT group may have had AR associated with a different allergen to grass pollen; however, because grass pollen is the cause of symptoms in almost two-thirds of AR cases [41], any potential bias should have been minimal. Patients with AR may also have been obtaining additional symptomatic relief by using OTC and other non-reimbursed AR medications, which are not recorded in the LRx database. This could possibly lead to overestimation of any treatment effect on the reduction in AR medication prescriptions; however, such a

potential bias should affect all patient groups in a comparable manner. The real-world study design itself may also have contributed to a dilution of the magnitude of any treatment effect, which would not be the case with a randomized controlled trial [33]. In addition, the SLIT tablet and non-AIT groups were only matched for treatment index year and so differed in some important respects (reflecting real life). The proportion of children and adolescents was markedly higher in the SLIT tablet group, as observed in an earlier German observational study [42], suggesting that physicians in Germany are more likely to prescribe SLIT tablets to younger patients.

The benefits of SLIT on AR progression, asthma occurrence, and asthma progression likely have health economic implications [28]. It would be of interest to further evaluate the potential impact on costs associated with SLIT use for 3 years, compared with recurrent use of symptomatic treatments for AR and AA, knowing that pre-coseasonal treatment regimens have economic and compliance benefits in comparison with perennial regimens [43].

Disease severity can influence treatment decisions under real-life conditions, leading to 'confounding by indication,' whereby a physician may preferentially prescribe a particular treatment to patients based on a perception of a different prognosis [33]. Such confounding was accounted for in the analyses of treatment effectiveness, but it may also be of interest in the future to assess whether patients treated with SLIT tablets may have had more severe symptoms than those in the non-AIT group.

5. Conclusions

The findings from this retrospective long-term database sub-analysis demonstrate the benefits of 5- and 1-grass-pollen SLIT tablets via slower progression of AR, reduced risk of new asthma onset in the non-asthmatic population, and slower asthma progression in the asthmatic population in real-world use. The study data are in line with the key recommendation from the most-recent EAACI guidelines on AIT for allergy prevention that a 3-year course of SLIT/SCIT can be recommended for children and adolescents with moderate to severe AR triggered by grass/birch pollen allergy to prevent asthma for up to 2 years post-AIT, in addition to its sustained effect on AR symptoms and medication [34].

Key issues

- Allergic rhinitis (AR) caused by grass pollen is associated with considerable morbidity and decreased quality of life worldwide, and is often comorbid with asthma.
- Allergy immunotherapy (AIT), in the form of subcutaneous or sublingual immunotherapy (SLIT) is the only disease-modifying intervention for AR. The 5- and 1-grass pollen SLIT tablets are currently licensed in the EU and US for the treatment of grass pollen-associated AR.
- Data from real-world studies on the progression of AR and/or asthma in patients receiving grass pollen SLIT tablets are sparse.

- In this subanalysis of a recent retrospective, real-world database analysis in Germany that followed patients for up to 6 years after treatment cessation, both SLIT formulations were associated with significant benefits compared to non-use of AIT, in the form of slower AR progression, reduced risk of new asthma onset in the non-asthmatic population, and slower asthma progression in the asthmatic population.

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