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Original Article

Long-term impact of a birch/alder/hazel or birch-only liquid sublingual immunotherapy on birch-family pollen respiratory allergy: A real-world study

Stefan Zielen [a, b, *], Hartmut Richter [c], Petra Zieglmayer [d], Michael Gerstlauer [e], Josiane Cognet-Sicé [f], Silvia Scurati [f], Philippe Devillier [g, h]

[a] Respiratory Research Centre, Medaimun GmbH, Frankfurt am Main, Germany
[b] Department of Paediatrics, University Hospital Frankfurt, Goethe-University, Frankfurt am Main, Germany
[c] Epidemiology, IQVIA, Frankfurt am Main, Germany
[d] Competence Centre for Allergology and Immunology, Karl Landsteiner University, Krems, Austria
[e] Paediatric and Adolescent Medicine, University Hospital Augsburg, Augsburg, Germany
[f] Stallergenes Greer, Antony, France
[g] Respiratory Pharmacology Research Unit, VIM Suresnes, UMR_0892, University Paris-Saclay, Suresnes, France
[h] Department of Airway Diseases, Hospital Foch, Suresnes, France

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AIT, allergen immunotherapy; AR, allergic rhinitis; CI, confidence interval; ENT, ear, nose and throat; ICS, inhaled corticosteroids; OR, odds ratio; SCIT, subcutaneous immunotherapy; SD, standard deviation; SLIT, sublingual immunotherapy

ABSTRACT

Background: Patients with allergic rhinitis (AR) and/or mild or moderate asthma derived from birch-family pollen allergy can be treated with liquid sublingual immunotherapy (SLIT-liquid). This study evaluated the impact of two SLIT extracts on AR and asthma progression or onset in these patients.
Methods: This was a sub-analysis of a retrospective, longitudinal comparative cohort study that used a German prescription database. Patients treated with 3-tree (birch/alder/hazel) or birch-only SLIT-liquid and followed up for up to 6 years after treatment were compared with controls dispensed symptomatic medications. Multiple regression analysis compared dispensation data as a proxy for disease status and progression.
Results: A total of 493 patients treated with 3-tree SLIT-liquid and 311 treated with birch SLIT-liquid were analysed vs. 44,835 patients included as controls. Overall, 70.5 % of patients presented solely AR, 24.2 % solely asthma, and 5.3 % both diseases. Compared with controls, patients treated with 3-tree SLIT-liquid had reduced risk of AR [odds ratio (OR) = 3.21, 95 % CI 2.54–4.06, $p < 0.001$], asthma progression (OR = 2.03, 95 % CI 1.43–2.89, $p < 0.0001$), or asthma onset (OR = 0.592, 95 % CI, 0.408–0.860, $p = 0.006$). Birch-only SLIT-liquid showed similar effectiveness in reducing AR and asthma medication dispensation but no significant effect in reducing new-onset asthma.
Conclusions: This real-world study demonstrated the effectiveness of treatment with 3-tree SLIT-liquid or birch SLIT-liquid in slowing the progression of birch-family pollen allergy. 3-tree SLIT-liquid covering a broader repertoire of epitopes mimicking natural exposure throughout the year may be valuable for patients sensitised to birch and/or alder and/or hazel pollen suffering from overlapping tree-pollen seasons.

Introduction

Allergic rhinitis (AR) is a chronic IgE-mediated hypersensitivity disorder characterised by the presence of rhinorrhoea, nasal congestion, sneezing, nasal and ocular pruritus (itching), and watery eyes.[1,2] AR is one of the most prevalent allergic diseases, affecting around a quarter of the world's population, and has had a rising trend in the past decades.[3] The burden of AR is high and associated with a considerable loss of quality of life and work productivity.[1] Seasonal AR is most often caused by plant allergens, which can be highly influenced by geographic location and time of year (e.g. tree pollens such as hazel, alder, birch, elm, maple, juniper, and olive are frequent causes of AR in spring). In northern Europe, birch pollen is one of the most common respiratory allergens.[4,5] Still, most birch pollen-sensitised patients also present

* Corresponding author. Respiratory Research Centre, Medaimun GmbH, Kennedyallee 97A, 60596 Frankfurt am Main, Germany.
E-mail address: s.zielen@medaimun.de (S. Zielen).
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sensitisations to pollen from alder and/or hazel due to partial but high allergen cross-reactivity.[6,7] In addition, overlapping tree pollen seasons considerably extend the symptomatic period experienced by AR patients.

Although AR and asthma are different diseases with distinct pathophysiological bases, they frequently coexist in the same patient, increasing the overall burden on patients and healthcare systems.[8,9] Treatment of AR could influence the development of asthma.[10] AR treatment options include pharmacotherapy to alleviate allergy symptoms, and allergen immunotherapy (AIT). By targeting the underlying pathophysiology, AIT is considered the only potentially disease-modifying treatment for AR available.[11] In addition to ameliorating symptoms and desensitising the patient, AIT can induce long-term clinical benefits that may persist for years after treatment discontinuation.[11,12] Additionally, AIT can prevent the onset of asthma in patients with AR.[13–15]

Subcutaneous and sublingual AIT (SCIT and SLIT, respectively) have been evaluated in randomised studies for the treatment of birch pollen-induced AR with or without asthma, demonstrating efficacy and safety.[16–22] Treatment with birch pollen AIT could be sufficient treatment for most patients with birch-tree family-induced AR,[23] as birch pollen AIT can modulate a cross-reactive IgE immune response to multiple related tree species such as alder and hazel.[24] However, as this cross-reactivity between birch-homologous allergens is high but only partial (around 85 %),[6,25] some patients sensitised to alder and/or hazel but not to birch pollen may not respond to isolated birch pollen AIT.

Real-world studies can complement randomised trials by providing long-term data on effectiveness and safety. In the case of AIT, these studies can also assess the preventative role of this therapy on allergic asthma onset and progression. In a real-world study based on a prescription database in Germany, the impact of six marketed products for birch or 3-tree (birch/alder/hazel) pollen AIT (SLIT or SCIT) was evaluated for pollen-induced AR progression, asthma onset, or asthma progression.[26] Records of patients who had received AIT plus symptomatic treatment were compared with controls who had received only symptomatic treatment. After up to 6 years of follow-up, significantly more AIT versus control patients were AR medication-free ($p < 0.001$), asthma medication-free ($p < 0.001$), and reduced existing asthma medication use ($p < 0.001$). Also, the new-onset asthma risk was significantly reduced in the AIT vs. control group (OR: 0.83; $p = 0.001$). This real-world study demonstrated the long-term benefits of AIT in patients with birch family pollen allergy. Still, the specific benefits of the 3-tree mixed pollen extracts over a birch pollen single extract for SLIT and over controls were not investigated.[26]

As a sub-analysis of this study, patients treated with 3-tree SLIT-liquid plus symptomatic treatment, or birch SLIT-liquid plus symptomatic treatment, were compared with matched controls with only symptomatic treatment to evaluate the impact of these SLIT extracts in patients with birch family pollen-allergy on prevention of disease progression and/or asthma onset.

Methods

Study design

This is a sub-analysis of a retrospective, longitudinal comparative cohort study that used a German prescription database to assess six AIT products available in Germany and indicated for birch family pollen AR and/or mild-moderate asthma.[26] The methodologies used in this study have been described in detail,[26] and a diagram of the study design is shown in Figure 1. Patients with AR and/or mild-moderate asthma who had undergone birch family pollen AIT were matched to patients who had received only symptomatic treatment. The index date was defined as the date of the first record of AIT between June 2009 and May 2013. For the control group, the index date was defined as the date of the second of three relevant prescriptions for AR in three consecutive 3-tree pollen seasons (same seasonal cycle as the matched patients). The pre-index period was defined as one year before the index date, and information on AR prescriptions and asthma status was collected in this period. The treatment period was defined as the time from the index date to the expiry date of the last prescription of the AIT. The follow-up period was from the end of the treatment period (AIT cessation) to the database lock in February 2017. Patients were followed up for 2–6 years after treatment cessation. In this sub-analysis, only patients who received the SLIT liquid extracts Staloral® Birch 300 IR/mL and Staloral® Birch/Alder/Hazel 300 IR/mL (Stallergenes Greer, Antony, France) were compared with their respective controls. Both products are indicated for AR and for mild to moderate allergic asthma.

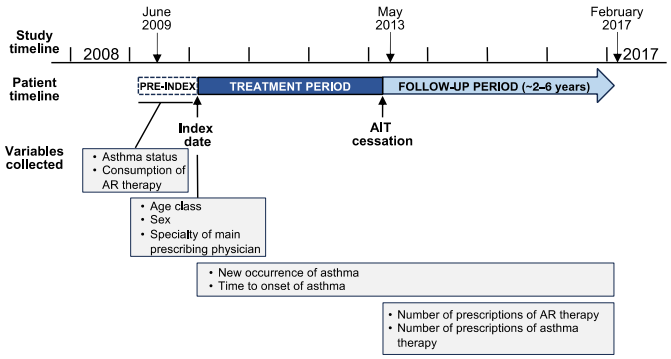

Fig. 1. Study design. AIT, allergen immunotherapy; AR, allergic rhinitis.

Database

The IQVIA™ LRx database (IQVIA, Frankfurt am Main, Germany) accesses nationwide pharmacy data collection centres processing prescription data of all German patients within the statutory health insurance system for reimbursement purposes, with a coverage of ~60 % of all prescriptions. Information collected is patient-related with a unique anonymised identification number, allowing patient follow-up. Data collected included patient age, gender, insurance company, and area of living, and prescription details as prescribers' anonymised identification number, date, and medication. In accordance with German legislation on the analysis of anonymised databases, informed consent was not required and approval by an ethics committee was not necessary. As the LRx database does not contain diagnosis information, prescription data were used as a proxy for disease onset and progression. Data covering nine pollen seasons (Jan 2008–Feb 2017) were extracted from two groups of patients: those with AR who received AIT products against 3-tree or birch pollen allergy and a control with AR and/or asthma due to 3-tree or birch pollen who had never received AIT.

Patients

Patients included in the AIT subgroups analysed here had the following criteria: ≥5 years; had received treatment in ≥2 successive 3-tree pollen seasonal cycles with 3-tree mix or birch alone SLIT-liquid extracts starting between June 2009 and May 2013; had ≥1 defining prescription against AR (nasal corticosteroids, oral/systemic antihistamines) in pre-index period and/or ≥2 defining

prescriptions against asthma [inhaled corticosteroids (ICS), ICS/long-acting beta-agonists, short-acting beta agonists] in the 3-tree pollen seasonal cycle defined by the index season or the one immediately preceding it; and ≥2 years of follow-up after AIT cessation. Patients were excluded if they had received any birch tree pollen AIT products in the 3-tree pollen seasonal cycle before the index date, or >1 of any birch tree pollen AIT products (the only exception was switching between birch and 3-tree pollen extracts inside one of the individual product groups), or any other AIT products against other pollen types (other tree, grass, weed …) or perennial allergens (house dust mites, animal dander …) in their entire database history. Patients were also excluded if they had severe asthma (treatment with biologics) or perennial asthma (defined as ≥3 prescriptions of ICS or methylxanthines, distributed over three successive 4-month periods before or over the pollen seasonal cycle of the index date) without exacerbations during the season.

The control group included patients with AR and/or asthma due to birch or 3-tree pollen who had not received any AIT in their entire database history. Patients in the control group were matched with those in the AIT group based on index year, number of seasonal cycles covered by the AIT, age group at index date, gender, main indication status at index date (AR, asthma, or both), and number of prescriptions of AR or asthma treatment in the pre-index period.

To ensure that all medications were actually prescribed for birch family pollen allergy, it was also required that at least the defining prescriptions were dispensed during the three-tree pollen season (February to May) or the month before it (January).

Endpoints and assessments

There were three primary endpoints in the study. First, the impact of AIT on the progression of AR from 2 to 6 years after AIT cessation (in patients with AR in the pre-index period, with or without asthma). The presence of AR symptoms was assessed by the consumption of AR symptomatic medication during the follow-up period. Second, the impact of AIT on the progression of asthma from 2 to 6 years after AIT cessation (in patients with asthma in the pre-index period, with or without AR). The presence of asthma symptoms was assessed by the consumption of asthma medication during the follow-up period. Third, the impact of AIT on asthma onset and development during AIT or up to 6 years after AIT cessation (in patients with AR but without asthma during the pre-index period). Asthma was assessed by the consumption of asthma medication in these periods.

Statistical analysis

The analyses were carried out using the statistical software SAS Version 9.4 (SAS Institute, Cary, NC, USA). Descriptive statistics were used for all outcome variables and covariates, and statistics are presented for numeric variables (N, mean, standard deviation).

The analyses of disease progression (AR or asthma) were carried out by regression using a general linear model, with the ratio of the annual number of prescriptions in the analysis period vs. the pre-index period used as the outcome variable. Since the probability of asthma occurrence would also depend on the length of the analytical timespan, the individual length of this period was included as a covariate. The analysis of asthma development as a Yes/No variable was achieved by logistic regression. The time to development of asthma was investigated using survival analysis (Kaplan–Meier). The pairwise comparison of the two 3-tree and birch SLIT liquid extracts was conducted post hoc. Statistical analyses were based on two-way testing without exception. For all statistical tests, the significance level was set to 5 % ($p \leq 0.05$).

Results

Of a total of 8967 patients with AR and/or mild-moderate asthma prescribed with AIT as identified in the LRx database, 493 (5.5 %) were dispensed 3-tree SLIT-liquid, and 311 (3.5 %) birch SLIT-liquid. A total of 44,835 patients who received only symptomatic treatment for AR were included as controls. The characteristics of these cohorts are shown in Table 1. Of the total population with AIT, 70.5 % presented solely AR, 24.2 % presented solely asthma, and 5.3 % both diseases. Most patients had been diagnosed by an ENT specialist (30.1 %) or a dermatologist (27.0 %), and only 12.3 % by a general practitioner. The mean follow-up duration for all patients was more than 4 years. There were no notable differences between both SLIT-liquid subgroups.

AR progression

Of the 6796 patients with AR with or without asthma, 386 (78.3 %) in the 3-tree SLIT-liquid group and 257 (82.6 %) in the birch SLIT-liquid group were dispensed AR symptomatic medication during the pre-index period, compared with 33,980 (75.8 %) controls (Table 1). Of these, the proportion of patients without AR symptomatic medication during the follow-up period was significantly higher among patients who had received 3-tree SLIT-liquid (74.6 %) or birch SLIT-liquid (74.3 %), compared with controls (47.3 %), with odds ratios (OR, 95 % CI) of 3.21 (2.54–4.06) and 3.20 (2.41–4.26), respectively ($p < 0.001$ for both) (Fig. 2A). Linear regression analysis showed that the AR symptomatic medication was reduced during the follow-up period by 32.5 % in patients who had received 3-tree SLIT-liquid and by 33.0 % in those who had received birch SLIT-liquid ($p < 0.001$ in both cases), compared with controls (Fig. 2B). No significant difference in the probability of becoming AR symptomatic medication-free was observed between the two SLIT-liquid allergen extracts (mix vs. single OR = 1.003, 95 % CI, 0.695–1.449, $p = 0.9860$).

Asthma progression

Of the 2642 patients with asthma or asthma and AR, 129 (26.2 %) in the 3-tree SLIT-liquid group and 65 (20.9 %) in the birch SLIT-liquid group were dispensed asthma symptomatic medication during the pre-index period, compared with 13,210 (29.5 %) controls (Table 1). Of these, the proportion of patients without asthma medication during the follow-up period was significantly higher among patients who had received 3-tree SLIT-liquid (54.3 %) or birch SLIT-liquid (52.3 %) compared with controls (35.1 %), with OR = 2.03 (95 % CI, 1.43–2.89; $p < 0.0001$) and OR = 2.00 (95 % CI, 1.22–3.29; $p = 0.006$), respectively (Fig. 3A). Compared with controls, asthma symptomatic medication was reduced during the follow-up period by 45.6 % in patients who had received 3-tree SLIT-liquid ($p < 0.001$), and by 31.8 % in those who had received birch SLIT-liquid ($p = 0.032$) (Fig. 3B). No significant difference in the probability of becoming asthma symptomatic medication-free was observed between the two SLIT-liquid products (OR = 1.013, 95 % CI, 0.553–1.858, $p = 0.9657$).

Asthma onset

Of the 6325 patients with AR and without asthma at baseline who received AIT, 789 developed asthma after the index date (500 patients during the treatment period and 289 during the follow-up). Of these, 31 patients had been treated with 3-tree SLIT-liquid

Table 1
Demographic, clinical and prescription-related characteristics of patients treated with AIT (all), 3-tree SLIT-liquid, birch SLIT-liquid, and controls at index date or during the pre-index period.

Variable	Total AIT (N = 8967)	3-tree SLIT (N = 493)	Birch SLIT (N = 311)	Controls (N = 44,835)
Age class (years), n (%)				
5-17	1784 (19.9)	109 (22.1)	76 (24.4)	8920 (19.9)
18-35	1934 (21.6)	89 (18.1)	66 (21.2)	9670 (21.6)
36-50	3073 (34.3)	151 (30.6)	98 (31.5)	15,365 (34.3)
>50	2176 (24.3)	144 (29.2)	71 (22.8)	10,880 (24.3)
Gender, n (%)				
Men	2717 (30.3)	161 (32.7)	102 (32.8)	13,585 (30.3)
Women	3537 (39.4)	189 (38.3)	116 (37.3)	17,685 (39.4)
Unknown	2713 (30.3)	143 (29.0)	93 (29.9)	13,565 (30.3)
Allergic disease, n (%)				
Allergic rhinitis	6325 (70.5)	364 (73.8)	246 (79.1)	31,625 (70.5)
Asthma	2171 (24.2)	107 (21.7)	54 (17.4)	10,855 (24.2)
Allergic rhinitis and asthma	471 (5.3)	22 (4.5)	11 (3.5)	2355 (5.3)
Prescribed symptomatic medication before index, n (%)				
AR medication	6796 (75.8)	386 (78.3)	257 (82.6)	33,980 (75.8)
Asthma medication	2642 (29.5)	129 (26.2)	65 (20.9)	13,210 (29.5)
Main prescribing physician specialty, n (%)				
ENT specialist	2695 (30.1)	146 (29.6)	113 (36.3)	6223 (13.9)
Dermatologist	2422 (27.0)	101 (20.5)	64 (20.6)	1940 (4.3)
Pneumologist	1330 (14.8)	48 (9.7)	17 (5.5)	1947 (4.3)
Paediatrician	934 (10.4)	31 (6.3)	29 (9.3)	4439 (9.9)
Internal specialist	415 (4.6)	21 (4.3)	13 (4.2)	6504 (14.5)
General practitioner	1102 (12.3)	136 (27.6)	65 (20.9)	23,296 (52.0)
Other specialty	69 (0.8)	10 (2.0)	10 (3.2)	486 (1.1)
Number of seasons of AIT, n (%)				
2	4045 (45.1)	190 (38.5)	125 (40.2)	20,225 (45.1)
3	3601 (40.2)	179 (36.3)	115 (37.0)	18,005 (40.2)
4	1189 (13.3)	111 (22.5)	64 (20.6)	5945 (13.3)
5	132 (1.5)	13 (2.6)	7 (2.3)	660 (1.5)
Follow-up (years), mean (SD)	4.41 (1.06)	4.37 (1.01)	4.28 (1.01)	4.16 (1.09)

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

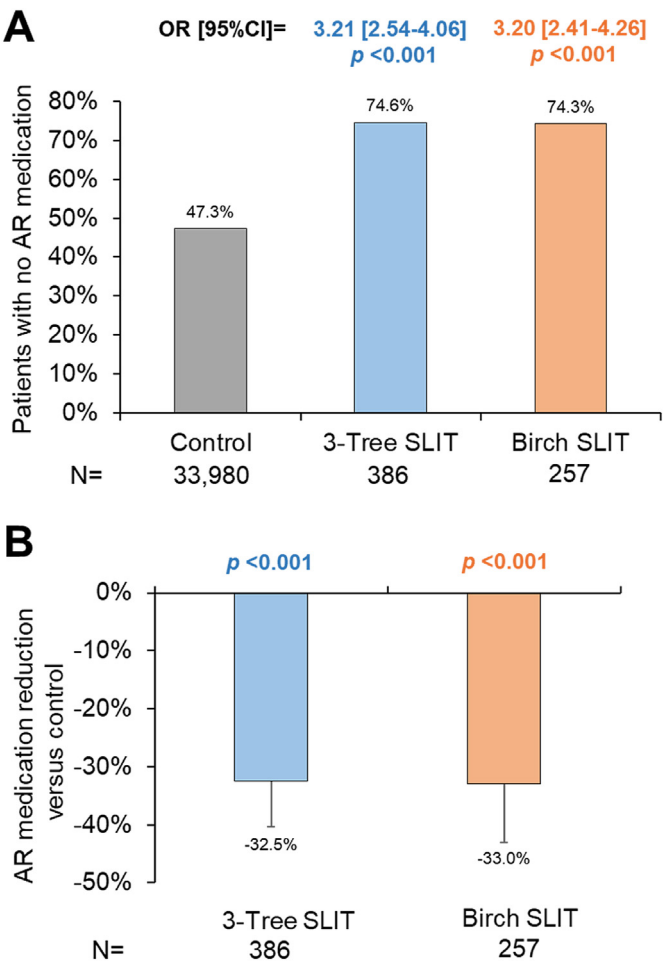

Fig. 2. Proportion of patients not dispensed AR symptomatic medication during follow-up (**A**). AR symptomatic medication dispensation reduction vs. control during follow-up (**B**). AIT, allergen immunotherapy; AR, allergic rhinitis; CI, confidence interval; OR, odds ratio; SLIT, sublingual immunotherapy.

(8.5 % of the 364 without asthma at baseline) and 26 with birch SLIT-liquid (10.6 % of the 246 without asthma), compared with 4148 controls (13.1 % of 31,563 without asthma) (Fig. 4A). Logistic regression showed that the risk of new asthma onset during treatment and follow-up was reduced significantly in patients treated with 3-tree SLIT-liquid, compared to controls (OR = 0.592; 95 % CI, 0.408–0.860; p = 0.006) (Fig. 4B). In patients previously treated with birch SLIT-liquid, however, this risk was not significantly reduced (OR = 0.776; 95 % CI, 0.514–1.172; p = 0.228). No significant difference in the probability of developing asthma was observed between the two SLIT-liquid products (mix vs. single OR = 0.763, 95 % CI, 0.439–1.327, p = 0.3383). The time to asthma occurrence for the 3 groups is presented in Figure 5. Mirroring the results of the logistic regression analyses, the curves show that patients treated with 3-tree or birch SLIT-liquid developed asthma at consistently lower rates than control patients, with a more favourable trend for 3-tree SLIT-liquid.

Discussion

The results of this sub-analysis of the retrospective longitudinal study published by Wahn *et al.* (2019)[26] reveal that, in patients with birch pollen-induced AR and/or asthma, 3-tree (birch/alder/hazel) mixed pollen SLIT-liquid showed significant real-world benefits during treatment and up to 6 years post-treatment cessation, preventing AR and asthma progression as well as new development of asthma. Birch single pollen SLIT-liquid showed similar effectiveness to 3-tree SLIT-liquid in reducing AR medication and, to a lesser extent, asthma medication, but no significant effect in reducing new-onset asthma. This study adds to the current body of evidence demonstrating the long-term benefit of SLIT-liquid for the treatment of patients with birch family pollen allergy.

Birch family pollen allergens induce broad and complex patterns of IgE cross-reactivity, with the major allergen Bet v 1 found to cross-react predominantly with extracts from alder, hornbeam, hazel, oak, chestnut, and beech homolog allergens, both in vitro and in vivo.[6,25,27] As a consequence, studies conducted in Germany reported a considerable proportion of patients (77 %–92 %) co-sensitised to birch, alder, and hazel pollen.[25,28] Overlapping tree pollen seasons considerably extend the symptomatic period for AR patients (from 2 to 3 up to 6 months, depending on the regions) by exposing them to multiple allergens over an extended timeframe.[5,6] In Europe, early hazel and alder season could prime sensitised patients for birch pollen later in the season, followed by allergic responses to beech and chestnut pollen.[4] In addition, climate change inducing increased pollen concentrations with greater allergenicity, prolonged pollen seasons, and the potential of long-range transport of pollen from distant regions can significantly modify pollinating seasons.[6,29] The cross-reactivity and extended exposure to birch-homologous allergens increases the overall burden on the immune system, potentially worsening the severity of symptoms and making management more challenging. By addressing multiple allergens simultaneously, 3-tree SLIT-liquid could offer significant benefits for individuals with AR triggered by multiple tree pollens,

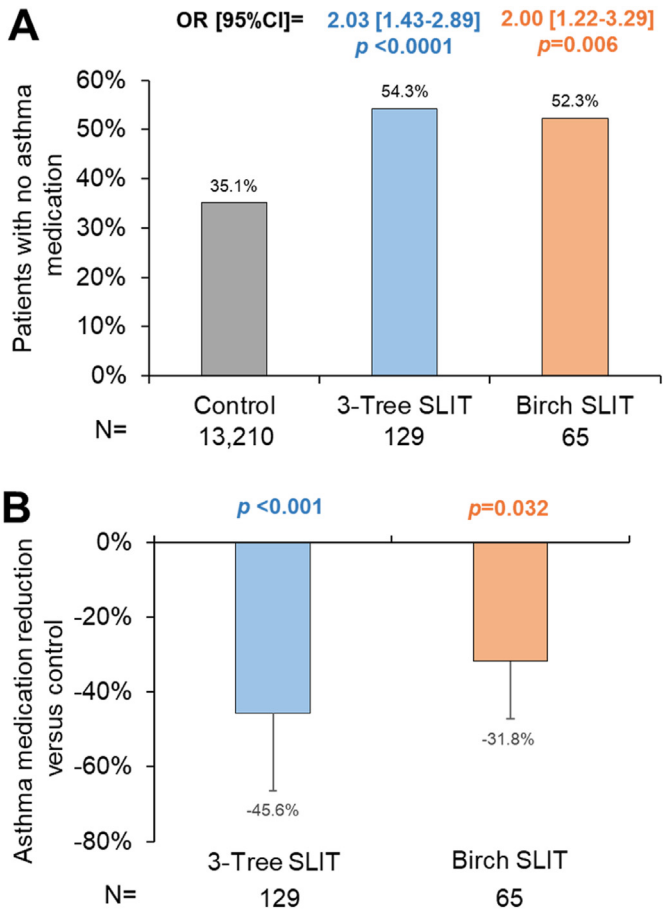

Fig. 3. Proportion of patients not dispensed asthma medication during follow-up (**A**), and asthma medication dispensation reduction vs. control during follow-up (**B**). AIT, allergen immunotherapy; CI, confidence interval; OR, odds ratio; SLIT, sublingual immunotherapy.

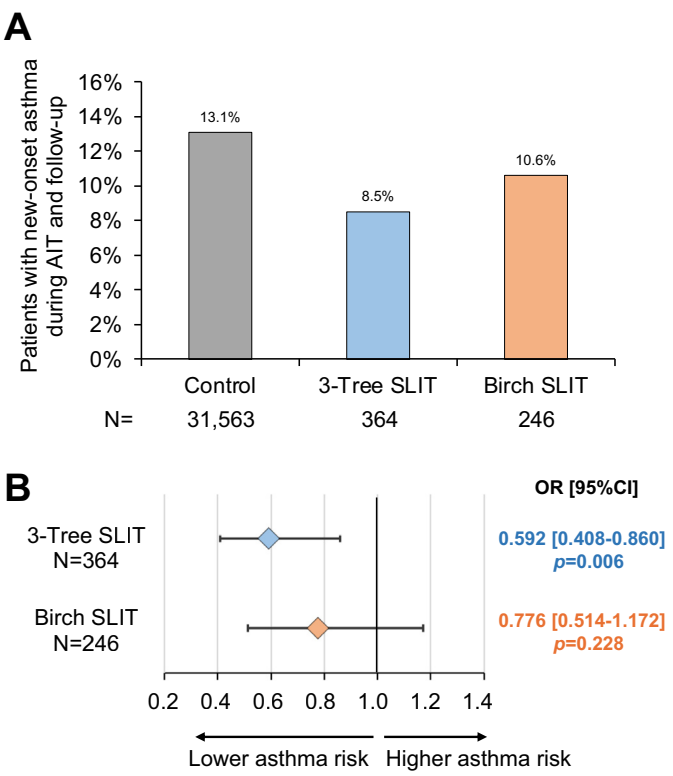

Fig. 4. Proportion of patients dispensed new asthma medication during treatment and follow-up (**A**), and risk of new asthma onset vs. control during treatment and follow-up (**B**). AIT, allergen immunotherapy; CI, confidence interval; OR, odds ratio; SLIT, sublingual immunotherapy.

simplifying treatment and potentially leading to lasting symptom relief for affected patients. This study shows that significantly more patients treated with 3-tree or birch SLIT-liquid became AR symptomatic medication-free than control patients during follow-up. The reduction in AR medication in patients treated with 3-tree SLIT or birch SLIT, compared to controls, was strong and very similar. These results are consistent with the ability of birch SLIT to confer cross-reactive symptom relief to multiple tree species.[23] Nevertheless, the cross-reactivity between birch-homologous allergens is not total, and depending on geographical locations or variations in individual sensitisation profiles, a non-negligible proportion of patients may not be efficiently covered by isolated birch AIT. In addition, several studies consistently reported rates of isolated sensitisation to hazel and/or alder (4 %–14 %).[25,30,31] This is in agreement with recent findings from Polak *et al.* suggesting a Bet v 1-independent sensitisation at T-cell level (particularly for alder pollen allergen Aln g 1) in individuals from birch tree-dominated areas.[32] Therefore, a combination of allergen extracts from pollen of the three tree species of the "Fagales group" with the greatest allergenic potency reflects the natural exposure and sensitisation conditions at the molecular level and provides a consistent and well-balanced composition of critical allergens, while extending the repertoire of T and B cell epitopes. Similarly, a 5-grass pollen SLIT-tablet was found to better cover the IgE epitope repertoire of pollen from the most common grasses in Europe, especially for patients from Southern Europe, than a 1-grass pollen SLIT-tablet.[33] In addition to this finding, a sub analysis of a retrospective, observational, prescription database study in Germany notably showed that, although no direct comparison was conducted, the 5-grass pollen SLIT tablet produced a somewhat greater reduction of symptomatic drug prescriptions for AR vs. non-AIT patients than the 1-grass pollen tablet on and up to 6 years post treatment.[34] Altogether, above data with birch and grass allergen families support the recommendations from an international group of clinician experts as to use for patients with AR due to allergens within a homologous group a single course of AIT with a mixture of allergens to cover a broader repertoire of epitopes for optimal reprogramming of the immune system.[35]

If the clinical implication of birch pollen on asthma onset remains debatable,[6] several studies in the past decade have shown positive associations between exposure to birch and the risk of developing asthma.[36–38] We found in our study around 30 % of birch allergic patients with pre-existing asthma, associated or not with AR. The number of patients who became free of asthma medication during the follow-up period was significantly higher among those treated with 3-tree SLIT-liquid compared with those in the control group. No significant differences were observed between the two SLIT-liquid extracts. However, in asthma medication reduction, the differences with control were more notable for patients treated with 3-tree SLIT-liquid than those treated with birch SLIT-liquid, and even greater than those observed in other AIT groups (natural SCIT, −37.3 %; allergoids, from −26.1 % to −33.7 %) in the original Wahn *et al.* study (2019).[26]

The constant exposure to birch family pollen allergens can exacerbate and extend inflammation to the lower respiratory tract, causing bronchial hyperreactivity and increasing the risk of developing asthma,[39] which can be further exacerbated by air pollution.[40] Early management of AR is crucial to prevent this progression. In this study, some patients with no asthma

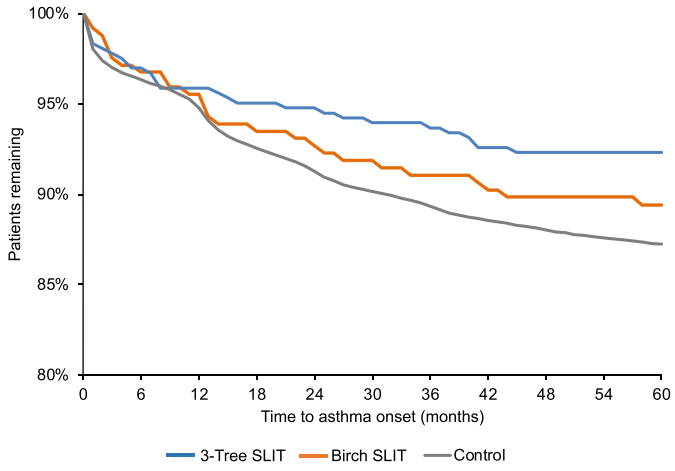

Fig. 5. Time to asthma occurrence in the non-asthmatic population for the full analysis period (Kaplan–Meier analysis). SLIT, sublingual immunotherapy.

medications during the pre-index period developed asthma during the treatment or follow-up periods.[26] However, compared with controls, those patients treated with 3-tree SLIT-liquid presented a lower risk of new-onset asthma. Those treated with birch SLIT-liquid also showed a favourable, albeit not significant, trend towards a reduction in the risk of developing asthma vs. controls. Noteworthy, the observed non-significance could be linked to low patient counts with this outcome and the associated lack of statistical power. In the Wahn *et al.* study (2019), there was also no significant reduction in the risk of new-onset asthma in patients treated with natural SCIT or allergoids during the 8-year analysis period.[26]

In this regard, the results of the SLIT groups presented in the current study are globally consistent with a recent population-based, real-world study that evaluated asthma onset and progression in AR patients with or without asthma treated with SLIT-liquid.[41] In this study, including 112,492 patients treated with SLIT (77,897 without pre-existing asthma) and 333,082 controls (235,547 without pre-existing asthma) with a long follow-up, exposure to SLIT-liquid in the non-asthmatic subpopulation was associated with a significantly lower risk of asthma onset compared to controls (HR = 0.77 [0.76–0.78] according to a sensitive definition of asthma events). For the 1744 patients mono-allergic to birch pollen, the adjusted hazard difference was −33 % versus controls. Further, this study showed the effectiveness of SLIT-liquid in preventing Global Initiative for Asthma (GINA) step-up treatment, regardless of asthma treatment step at baseline, in patients with pre-existing asthma.[41] Other studies have shown that the preventive effect of AIT in asthma onset, independently of allergen type, is especially notorious in children who completed at least three years of AIT, and in mono-sensitised patients.[42] The real-world evidence study presented here, specifically in birch family pollen allergy, supports the benefits of SLIT-liquid in the progression of AR and the progression or onset of moderate asthma. It substantiates a general analysis of studies of the long-term effectiveness outcomes of AIT based on prescription databases by various allergens, which confirmed results in randomised trials.[41,43]

The interpretation of the results of this study presents some limitations that must be considered. The main one was the lack of diagnosis references in the database; for this reason, the treatment had to be used as a proxy to identify the disease. Also, as with any database study, there was a risk of misidentifying patients. This could have led to an underestimation of the number of AR patients, as allergy medications (e.g. antihistamines) often do not require a prescription and would not be recorded in the database. This possibility could have affected the results of the patient selection process and the assessment of AR progression. However, it is expected that this potential bias would have affected both study groups to an equal degree so that the relative comparisons of the two groups and the conclusions drawn here from them are valid. Another potential limitation is the possible overlap of birch family allergy season with other allergens, such as grass. As methodological strengths, including important variables in the matching process between SLIT-treated patients and controls (especially age, treatment period duration, and baseline treatment levels) has contributed to the robustness of the conclusions. Also, the real-world data source, and the long-term follow-up, reinforce the results regarding the effectiveness of these SLIT mixed and single extracts.

In conclusion, this real-world study showed the effectiveness of treatment with 3-tree SLIT-liquid or birch SLIT-liquid in slowing the progression of both birch(/alder/hazel) pollen-induced AR up to 6 years post-treatment cessation. Though direct comparison indicated no significant differences between both SLIT mixed and single extracts, 3-tree SLIT-liquid appeared to provide long-term benefits in asthma, both in terms of halting its progression and in preventing its onset. SLIT-liquid with 3-tree mix pollen extracts covering a broader repertoire of epitopes may be of great value for patients sensitised to birch and/or alder and/or hazel pollen suffering from overlapping tree pollen seasons which considerably extend the symptomatic period. Furthermore, patients not sensitised to birch but to alder and/or hazel pollen can benefit from this combined tree pollen extracts mixture which mimics natural exposure throughout the year.

With regards to the clinical implications of our findings when using SLIT-liquid, we suggest that patients exclusively sensitised to birch be treated with birch allergen alone while patients sensitised to birch, alder and/or hazel, whether polysensitisation is known or unknown (skin prick test or specific-IgE results for alder and hazel not available), be treated with 3-tree SLIT-liquid to ensure better coverage.

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Conflict of Interest

SZ declares having received support for article processing charge from Stallergenes Greer. HR is an employee of IQVIA GmbH & Co. OHG, which was contracted to conduct the analyses using their database IQVIA LRx; he has received no additional payments associated with the study over and above his salary. JCS and SS are employees of Stallergenes Greer. PD declares having received support for study funding, medical writing and article processing charge from Stallergenes Greer. The rest of the authors have no conflict of interest.

Authors' contributions

SZ, HR, SS, PD conceptualized the study. HR was involved in the methodology, data analysis and interpretation. JCS was involved in the writing of the original draft with support from Francisco López de Saro (Trialance SCCL). SS supervised the project. All authors were involved in the critical revision of the manuscript. All authors approved the final version of the manuscript for publication.

References

1. Bousquet J, Anto JM, Bachert C, Baiardini I, Bosnic-Anticevich S, Canonica GW, et al. Allergic rhinitis. *Nat Rev Dis Primers* 2020;**6**:95.

2. Wise SK, Damask C, Roland LT, Ebert C, Levy JM, Lin S, et al. International consensus statement on allergy and rhinology: allergic rhinitis - 2023. *Int Forum Allergy Rhinol* 2023;**13**:293–859.
3. Akdis CA, Agache I, Hellings P. *Global Atlas of Allergic Rhinitis and Chronic Rhinosinusitis*. Switzerland: European Academy of Allergy and Clinical Immunology; 2015. Available at: https://hub.eaaci.org/education_books/global-atlas-of-allergic-rhinitis-and-chronic-rhinosinusitis/. [Accessed 17 June 2024].
4. D'Amato G, Cecchi L, Bonini S, Nunes C, Annesi-Maesano I, Behrendt H, et al. Allergenic pollen and pollen allergy in Europe. *Allergy* 2007;**62**:976–90.
5. Raith M, Swoboda I. Birch pollen-The unpleasant herald of spring. *Front Allergy* 2023;**4**:1181675.
6. Biedermann T, Winther L, Till SJ, Panzner P, Knulst A, Valovirta E. Birch pollen allergy in Europe. *Allergy* 2019;**74**:1237–48.
7. Wang X, Chen L, Ding J, Wang H, Wang X. Profiles of birch allergen component sensitization and its association with pollen food allergy syndrome in northern China. *J Asthma Allergy* 2023;**16**:1241–50.
8. Miller RL, Grayson MH, Strothman K. Advances in asthma: new understandings of asthma's natural history, risk factors, underlying mechanisms, and clinical management. *J Allergy Clin Immunol* 2021;**148**:1430–41.
9. Bousquet J, Melén E, Haahtela T, Koppelman GH, Togias A, Valenta R, et al. Rhinitis associated with asthma is distinct from rhinitis alone: the ARIA-MeDALL hypothesis. *Allergy* 2023;**78**:1169–203.
10. Brozek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines-2016 revision. *J Allergy Clin Immunol* 2017;**140**:950–8.
11. Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, Gerth van Wijk R, et al. EAACI guidelines on allergen immunotherapy: allergic rhinoconjunctivitis. *Allergy* 2018;**73**:765–98.
12. Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica GW, et al. International consensus on allergy immunotherapy. *J Allergy Clin Immunol* 2015;**136**:556–68.
13. Schmitt J, Schwarz K, Stadler E, Wüstenberg EG. Allergy immunotherapy for allergic rhinitis effectively prevents asthma: results from a large retrospective cohort study. *J Allergy Clin Immunol* 2015;**136**:1511–6.
14. Zielen S, Devillier P, Heinrich J, Richter H, Wahn U. Sublingual immunotherapy provides long-term relief in allergic rhinitis and reduces the risk of asthma: a retrospective, real-world database analysis. *Allergy* 2018;**73**:165–77.
15. Arshad SH. Does allergen immunotherapy for allergic rhinitis prevent asthma? *Ann Allergy Asthma Immunol* 2022;**129**:286–91.
16. Khinchi MS, Poulsen LK, Carat F, André C, Hansen AB, Malling H-J. Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. *Allergy* 2004;**59**:45–53.
17. Voltolini S, Troise C, Incorvaia C, Bignardi D, Di Cara G, Marcucci F, et al. Effectiveness of high dose sublingual immunotherapy to induce a stepdown of seasonal asthma: a pilot study. *Curr Med Res Opin* 2010;**26**:37–40.
18. Worm M, Rak S, de Blay F, Malling H-J, Melac M, Cadic V, et al. Sustained efficacy and safety of a 300IR daily dose of a sublingual solution of birch pollen allergen extract in adults with allergic rhinoconjunctivitis: results of a double-blind, placebo-controlled study. *Clin Transl Allergy* 2014;**4**:7.
19. Bożek A, Kołodziejczyk K, Jarząb J. Efficacy and safety of birch pollen immunotherapy for local allergic rhinitis. *Ann Allergy Asthma Immunol* 2018;**120**:53–8.
20. Mäkelä MJ, Gyllfors P, Valovirta E, Steffensen MA, Grønager PM, Savolainen J, et al. Immunotherapy with the SQ tree SLIT-tablet in adults and adolescents with allergic rhinoconjunctivitis. *Clin Ther* 2018;**40**:574–86.e4.
21. Pfaar O, Bachert C, Kuna P, Panzner P, Džupinová M, Klimek L, et al. Sublingual allergen immunotherapy with a liquid birch pollen product in patients with seasonal allergic rhinoconjunctivitis with or without asthma. *J Allergy Clin Immunol* 2019;**143**:970–7.
22. Biedermann T, Kuna P, Panzner P, Valovirta E, Andersson M, de Blay F, et al. The SQ tree SLIT-tablet is highly effective and well tolerated: results from a randomized, double-blind, placebo-controlled phase III trial. *J Allergy Clin Immunol* 2019;**143**:1058–66.e6.
23. Kleine-Tebbe J, Zuberbier T, Werfel T, Krüll M, Wagenmann M, Johansen N, et al. Is allergy immunotherapy with birch sufficient to treat patients allergic to pollen of tree species of the birch homologous group? *Allergy* 2020;**75**:1327–36.
24. Würtzen PA, Grønager PM, Lund G, Gupta S, Andersen PS, Biedermann T, et al. Simplified AIT for allergy to several tree pollens-Arguments from the immune outcome analyses following treatment with SQ tree SLIT-tablet. *Clin Exp Allergy* 2021;**51**:284–95.
25. Beutner C, Werchan B, Forkel S, Gupta S, Fuchs T, Schön MP, et al. Sensitization rates to common inhaled allergens in Germany - increase and change patterns over the last 20 years. *J Dtsch Dermatol Ges* 2021;**19**:37–44.
26. Wahn U, Bachert C, Heinrich J, Richter H, Zielen S. Real-world benefits of allergen immunotherapy for birch pollen-associated allergic rhinitis and asthma. *Allergy* 2019;**74**:594–604.
27. Niederberger V, Pauli G, Grönlund H, Fröschl R, Rumpold H, Kraft D, et al. Recombinant birch pollen allergens (rBet v 1 and rBet v 2) contain most of the IgE epitopes present in birch, alder, hornbeam, hazel, and oak pollen: a quantitative IgE inhibition study with sera from different populations. *J Allergy Clin Immunol* 1998;**102**(Pt 1):579–91.
28. Canis M, Groger M, Becker S, Klemens C, Kramer MF. Recombinant marker allergens in diagnosis of patients with allergic rhinoconjunctivitis to tree and grass pollens. *Am J Rhinol Allergy* 2011;**25**:36–9.
29. Verstraeten WW, Bruffaerts N, Kouznetsov R, De Weger L, Sofiev M, Delcloo AW. Attributing long-term changes in airborne birch and grass pollen concentrations to climate change and vegetation dynamics. *Atmos Environ* 2023;**298**:119643.
30. Mari A, Wallner M, Ferreira F. Fagales pollen sensitization in a birch-free area: a respiratory cohort survey using Fagales pollen extracts and birch recombinant allergens (rBet v 1, rBet v 2, rBet v 4). *Clin Exp Allergy* 2003;**33**:1419–28.
31. Eder K, Markmann S, Gellrich D, Mann S-L, Högerle C, Gröger M. Does the principle of homologous groups allow a reduction of allergens in the skin prick test panel? *Eur Arch Otorhinolaryngol* 2021;**278**:117–25.
32. Polak D, Vollmann U, Grilo J, Bogdanov IV, Aglas L, Ovchinnikova TV, et al. Bet v 1-independent sensitization to major allergens in Fagales pollen: evidence at the T-cell level. *Allergy* 2023;**78**:743–51.
33. Batard T, Sanjuan A, Denis L, Nguyen H, Montagut A, Sastre J, et al. Two grass pollen tablets commercially available for allergy immunotherapy display different IgE epitope repertoires. *Clin Transl Allergy* 2019;**9**:13.
34. Devillier P, Wahn U, Zielen S, Heinrich J. 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. *Expert Rev Clin Immunol* 2017;**13**:1199–206.
35. Demoly P, Passalacqua G, Pfaar O, Sastre J, Wahn U. Management of the polyallergic patient with allergy immunotherapy: a practice-based approach. *Allergy Asthma Clin Immunol* 2016;**12**:2.
36. Guilbert A, Cox B, Bruffaerts N, Hoebeke L, Packeu A, Hendrickx M, et al. Relationships between aeroallergen levels and hospital admissions for asthma in the Brussels-Capital Region: a daily time series analysis. *Environ Health* 2018;**17**:35.
37. Lappe BL, Ebelt S, D'Souza RR, Manangan A, Brown C, Saha S, et al. Pollen and asthma morbidity in Atlanta: A 26-year time-series study. *Environ Int* 2023;**177**:107998.
38. Lindqvist M, Leth-Moller KB, Linneberg A, Kull I, Bergström A, Georgellis A, et al. Natural course of pollen-induced allergic rhinitis from childhood to adulthood: a 20-year follow up. *Allergy* 2024;**79**:884–93.
39. Gherasim A, Dietsch F, Beck M, Domis N, De Blay F. Asthma responses in birch allergic rhinitis (AR) with and without known birch-related asthma. *J Allergy Clin Immunol* 2023;**151**:AB188.
40. Carlsen HK, Haga SL, Olsson D, Behndig AF, Modig L, Meister K, et al. Birch pollen, air pollution and their interactive effects on airway symptoms and peak expiratory flow in allergic asthma during pollen season - a panel study in Northern and Southern Sweden. *Environ Health* 2022;**21**:63.
41. Demoly P, Molimard M, Bergmann J-F, Delaisi B, Gouverneur A, Vadel J, et al. Impact of liquid sublingual immunotherapy on asthma onset and progression in patients with allergic rhinitis: a nationwide population-based study (EfficAPSI study). *Lancet Reg Health Eur* 2024;**41**:100915.
42. Farraia M, Paciência I, Castro Mendes F, Cavaleiro Rufo J, Shamji M, Agache I, et al. Allergen immunotherapy for asthma prevention: a systematic review and meta-analysis of randomized and non-randomized controlled studies. *Allergy* 2022;**77**:1719–35.
43. Vogelberg C, Klimek L, Brüggenjürgen B, Jutel M. Real-world evidence for the long-term effect of allergen immunotherapy: current status on database-derived European studies. *Allergy* 2022;**77**:3584–92.