Impact of liquid sublingual immunotherapy on asthma onset and progression in patients with allergic rhinitis: a nationwide population-based study (EfficAPSI study)

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Summary

Background The only disease-modifying treatment currently available for allergic rhinitis (AR) is allergen immunotherapy (AIT). The main objective of the EfficAPSI real-world study (RWS) was to evaluate the impact of liquid sublingual immunotherapy (SLIT-liquid) on asthma onset and evolution in AR patients.

Methods An analysis with propensity score weighting was performed using the EfficAPSI cohort, comparing patients dispensed SLIT-liquid with patients dispensed AR symptomatic medication with no history of AIT (controls). Index date corresponded to the first dispensation of either treatment. The sensitive definition of asthma event considered the first asthma drug dispensation, hospitalisation or long-term disease (LTD) for asthma, the specific one omitted drug dispensation and the combined one considered omalizumab or three ICS ± LABA dispensation, hospitalisation or LTD. In patients with pre-existing asthma, the GINA treatment step-up evolution was analysed.

Findings In this cohort including 112,492 SLIT-liquid and 333,082 controls, SLIT-liquid exposure was associated with a significant lower risk of asthma onset *vs.* control, according to all definitions (combined: HR [95% CI] = 0.62 [0.60–0.63], sensitive: 0.77 [0.76–0.78], and specific: 0.67 [0.61–0.72]). Exposure to SLIT was associated with a one-third reduction in GINA step-up regardless baseline steps.

Interpretation In this national RWS with the largest number of person-years of follow-up to date in the field of AIT, SLIT-liquid was associated with a significant reduction in the risk of asthma onset or worsening. The use of three definitions (sensitive or specific) and GINA step-up reinforced the rigorous methodology, substantiating SLIT-liquid evidence as a causal treatment option for patients with respiratory allergies.

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Keywords: Asthma; Rhinitis; Allergic; Sublingual immunotherapy; Precision medicine

Introduction

Worldwide, allergic rhinitis (AR) affects 400 million people, and in France, the prevalence of AR ranges from 20% to 30% of the population, with significant regional and age differences. Of these, one third have concomitant allergic asthma.[1–3] AR and allergic asthma are a public health concern because of their increasing prevalence, the significant impact on patients' quality of life and the growing associated burden of disease.[4]

Global AR management aims at controlling symptoms and reducing inflammation. If allergen avoidance is not effective or feasible, oral or nasal antihistamines

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Research in context

Evidence before this study

Randomised controlled trials (RCTs) and observational studies have confirmed the efficacy and safety of allergen immunotherapy (AIT) in patients with allergic rhinitis (AR) with or without asthma. However, data on the impact of AIT on asthma onset and worsening prevention remained scarce. We searched MEDLINE and EMBASE from 1 January 2004 to 1 January 2024 for reports in English using the following search terms in Title/Abstract: ("sublingual" OR "SLIT") AND ("asthma" AND "immunotherapy"), limited to human studies. The search yielded 475 publications. Following review, we excluded editorials, background articles, guidelines, reviews, case reports and publication types of no interest, mechanistic or pharmaco-economic studies, and studies with drugs or outcomes of no interest to our question. From the remaining 32 publications, we retained original researches and most recent meta-analyses discussing AIT and its impact on asthma prevention. Noteworthy, a number of real-word studies (RWSs) reported data for a limited number of patients and/or short follow-up period. For the purpose of discussing the findings of our study, we identified from our search key prospective RCTs (n = 7) and retrospective RWSs with large populations and long-term follow-up (n = 8) addressing more specifically the potential preventive effect of AIT on asthma onset and/or progression in patients with AR with or without asthma.

Added value of this study

In the national real-world EfficAPSI study with the largest number of person-years of follow-up to date in the field of AIT, personalised SLIT-liquid (Stallergenes Greer, Antony, France) was associated with a significant reduction in the risk of new asthma events for up to eight years. Multiple stratification confirmed the effectiveness of SLIT-liquid in preventing asthma or reducing the risk of an asthma worsening, for all ages and allergens evaluated. The evaluation of three event definitions, more or less sensitive and specific, and of the GINA treatment step evolution reinforced the rigorous methodology used for our research. This and the completeness of the data with on- and post-treatment follow-up allow a more robust and consistent evaluation of the impact of this SLIT-liquid on asthma in real-life to complete the existing evidence.

Implications of all the available evidence

Allergic asthma is a public health concern because of its increasing prevalence, the significant impact on patients' quality of life and the growing associated burden of disease. There remains a need for data on impact of AIT on asthma onset and worsening prevention. Our research involving the largest number of person-years of follow-up to date in AIT and a rigorous and reinforced methodology provides important insights about SLIT-liquid as asthma disease-modifying medicine. Our findings support the long-term effectiveness of personalised SLIT-liquid in real-life for the treatment of AR patients with and without pre-existing asthma, and substantiate its evidence as a relevant causal treatment option for patients with respiratory allergies, for all ages and allergens considered, with abilities to prevent both disease onset and progression.

(AH) or intranasal corticosteroids (INCS) are recommended as first-line treatment. If the response is inadequate or absent, allergen immunotherapy (AIT), the only causal treatment for respiratory allergies, may be indicated in combination with pharmacotherapy.[5,6] As recommended, AIT should be administered for at least three years, either subcutaneously (SCIT) or sublingually (SLIT) with tablets or liquid formulations.[3,7,8] The management of allergic asthma is based on the Global Initiative for Asthma (GINA) treatment guidelines, and mainly requires inhaled corticosteroids (ICS) with or without long-acting beta2-agonists (LABA).[9]

Randomised controlled trials (RCTs) have demonstrated that SLIT liquid or tablet formulations (mainly including grass, birch and/or mite allergen extracts) may prevent the development or progression of asthma in patients with seasonal or perennial AR without or with asthma.[10–16] The trials notably showed the efficacy of SLIT in preventing or reducing asthma symptoms and ICS use and decreasing the risk of moderate-to-severe asthma exacerbations. Retrospective longitudinal observational studies in real-world settings confirmed that SLIT was associated with reduced risk of new asthma onset and/or long-term reductions in asthma medication dispensations, asthma exacerbations, pneumonia and hospitalisations.[17–25] However, they often reported data with both liquid and tablets or tablets only.

SLIT-liquid is a targeted treatment, specifically developed and adapted for a patient to treat their specific allergies taking into account their own immunological profile and response to treatment.[26,27] The evaluation of this promising personalised treatment for two of the most prevalent and debilitating diseases in the world is necessary and essential in the public health interest, to raise awareness among public decision-makers and to maintain public coverage for patients. A recent publication describing the methodology has shown that the EfficAPSI cohort is currently the largest one in the field and the most accurate for the evaluation of this product.[28] Here, the aim is to present the main objective of the EfficAPSI study: the evaluation of the real-world impact of personalised SLIT-liquid on the prevention of asthma onset or worsening in treated AR patients without or with asthma, respectively.

Methods

Data sources

The data sources and the methodology used to select patients in the EfficAPSI cohort have been described in detail in a previous publication.[28] Two nationwide databases, the Stallergenes Greer's (Antony, France) dispensing registry (including all patients treated with Staloral® SLIT-liquid in France) and the French national health data system SNDS (including data of 98.8% of the French population), were linked to form the national EfficAPSI cohort of patients with treated AR with or without asthma. The study protocol was approved by the "*Comité d'expertise pour les recherches, les études et les évaluations dans le domaine de la santé*" (CERESS; file number 790257) and "*Commission Nationale de l'Informatique et des Libertés*" (CNIL; file number 919412). In line with the European General Data Protection Regulation (GDPR), all individuals in the Stallergenes Greer database were informed of the present study and were given the opportunity to opt out from the use of their data. Subsequently, all patients who opted out were excluded from the study. Regarding data from the SNDS database, the *Caisse nationale de l'Assurance Maladie* (CNAM), as data controller, was responsible for patient information.

Study population

Patients who initiated treatment with SLIT-liquid (Staloral®) as identified in the Stallergenes Greer database were considered exposed, and patients dispensed AR symptomatic medication (consequently without any history of AIT) were considered controls. The index date was the date of the first dispensation of SLIT-liquid or AR medication, respectively (Appendix Methods S1 for codes). All inclusion and exclusion criteria have been detailed in the Appendix Methods S2.[28]

The inclusion period ran from January 1st, 2010 to December 31st, 2013. The look-back period was the four years before the index date. All patients were followed from the index date until death from any cause, loss to follow-up (defined as absence from reimbursed care for 12 consecutive months), or the end of the study (December 31st, 2018), whichever came first. For survival analyses, controls were censored while AIT was initiated during follow-up.

Endpoints

The primary endpoint was the occurrence of new asthma events over the study period. To minimise any bias that might be associated with this "*a priori*" definition, and to increase the consistency and robustness of the analyses, several more or less stringent definitions of events were used in the analyses.

The 'sensitive definition', very sensitive but not specific, considered the first dispensation of an asthma medication available at the time of the study conduct (short-acting beta2-agonist [SABA], ICS, LABA, antileukotriene, xanthine or omalizumab) or a hospitalisation for asthma or a long-term disease (LTD) for severe asthma. The 'specific definition', more specific but less sensitive, omitted medication dispensations considering only hospitalisation or LTD for severe asthma. The 'combined definition', both sensitive and specific, considered the dispensations of specific major asthma medications (omalizumab or three ICS ± LABA), hospitalisation or LTD for severe asthma (for hospitalisation or LTD: ICD-10 code J45 or J46, for medications see Appendix Methods S1). To evaluate the effect on the progression of asthma in patients with pre-existing asthma at index date, GINA recommendations were followed to determine the highest treatment step for each patient in each year.[9] Given the difficulty of classifying patients receiving treatment steps 3 and 4 which differ only in ICS dose, these were grouped (see Appendix Methods S3 for GINA steps). An increase in treatment step from baseline was considered an event. Patients receiving the highest treatment step at baseline (step 5) were excluded from the analysis since they could not experience the event.[29]

Statistical analyses

To describe the study population, quantitative variables were reported as mean, standard deviation, median, and interquartile range [IQR]. Categorical variables were reported as frequency and percentage.

To limit the impact of confounding and to account for the likely indication bias in comparative analyses, the models were weighted using the inverse probability of treatment weighting (IPTW), as previously described.[28] The probability of being treated with Staloral® was determined for each patient from the propensity score estimated using a logistic regression adjusted for all the following patient characteristics at baseline: year of index date, demographics, comorbidities, antibiotic dispensation, AR and asthma treatments (see Appendix Methods S4 for variables). The impact of SLIT-liquid on the occurrence of a new asthma event (according to new asthma event definitions or GINA treatment step) was evaluated using a Cox proportional hazards regression model and proportional hazard assumption was assessed. Adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated through IPTW and models were adjusted for variables that remained unbalanced after weighting (standardised mean differences > 0.1), and for treatment dispensation and pneumologist and paediatrician consultations as one-year time-varying variables (see Appendix Methods S3 for variables). Since the GINA treatment step at baseline could influence the risk of an increase in treatment step, analyses were stratified by the baseline GINA step.

All analyses were performed in the overall EfficAPSI cohort to evaluate the impact of SLIT-liquid on new asthma events as well as in the subgroups of patients without or with pre-existing mild-to-moderate asthma at

index date to evaluate the impact on asthma onset or worsening, respectively. Furthermore, the following stratified analyses were performed: (i) stratification by age in class ([5–24]; [25–39]; [40–49] and ≥50 years old); (ii) stratification by major allergens sensitizations, only known in the SLIT-liquid group (HDM, grass, birch, ragweed, cat, and *Alternaria*). *Post-hoc* analyses were performed: (i) on children ([5–17] years old); (ii) on other adults' age classes ([18–39], [40–44] and ≥45 years old); (iii) stratification by sex (female and male); (iv) sensitive, specific, and combined definitions on patients with pre-existing asthma; and (v) GINA step-down. To take into account the risk of misclassification due to nonadherence, the step-down was evaluated annually by identifying the higher GINA treatment step each year and comparing it to the baseline GINA step. Adjusted odds ratios (OR) and 95% CI were estimated through logistic regression models with IPTW and adjusted for variables that remained unbalanced after weighting (standardised mean differences > 0.1), and for treatment dispensation in the year preceding the index date.

All analyses were performed with SAS statistical software (version 9.4; SAS Institute, Cary, NC, USA).

Role of funding source

This work was sponsored by Stallergenes Greer. Laurence Girard and Silvia Scurati (Stallergenes Greer), Amandine Gouverneur, Jade Vadel and Cédric Collin (IQVIA), together with Pascal Demoly, Mathieu Molimard, Jean-François Bergmann, Bertrand Delaisi and Philippe Devillier, were involved in designing the study, collecting and interpreting the data, writing and revising the article and deciding to submit it for publication. Amandine Gouverneur, Jade Vadel and Cédric Collin (IQVIA) were involved in the data analysis.

Results

Description of the population

Of the 445,574 patients enrolled in the EfficAPSI cohort, 112,492 were exposed to SLIT-liquid and 333,082 were considered controls (Appendix Results S1).[28] Exposed patients were significantly younger than controls (mean 37.8 *vs.* 38.8 years) and more likely to be men (44.0% *vs.* 39.9%). They were less likely to benefit from the *couverture maladie universelle complémentaire* (CMUc *i.e.,* total coverage of health expenses by the public health insurance system associated with low-income issue) (5.3% *vs.* 13.3%) and less likely to have comorbidities, particularly anxiety (6.7% *vs.* 14.2%), depression (6.9% *vs.* 11.0%) and GERD (8.2% *vs.* 17.1%). They had a lower mean number of AH or INCS dispensed, but a higher mean number of AH and INCS dispensed together. A third of patients in both groups had a history of mild-to-moderate asthma (30.8% and 29.3%, respectively). Among the exposed patients, two thirds (68.6%) of patients were treated for a single allergy, mainly HDM (32.7%) and grass pollen (14.0%) (Table 1 and Appendix Results S3). After IPTW, the characteristics of patients in both cohorts were similar (Appendix Results S2).

The median follow-up was 6.9 years for exposed patients and 8.2 years for controls.

Overall population: association between new asthma events and SLIT exposure

In overall EfficAPSI cohort, the crude incidence of new asthma event using the sensitive definition was 13.9 per 100 person-years for the exposed group (n = 112,492) and 17.4 per 100 person-years for the control group (n = 333,082). Using the specific definition, it was 0.3 per 100 person-years for the exposed group and 0.5 per 100 person-years for the control group. And finally, using the combined definition, it was 2.4 per 100 person-years and 3.6 per 100 person-years for the exposed and control groups, respectively (Table 2).

Compared to controls, exposure to SLIT-liquid was found to be associated with a significant 36% reduction in new asthma events based on the combined definition (HR [95% CI]: 0.64 [0.63–0.65]). The reduction was approximately 24% for the sensitive definition and 34% for the specific definition (HR [95% CI]: 0.76 [0.75–0.76] and 0.66 [0.63–0.69], respectively); (Table 2 and Fig. 1). The results were consistent across age groups ranging from 33 to 44%, with a greater reduction observed in younger patients (5–24 years, HR [95% CI]: 0.56 [0.54–0.58], combined definition) or children (0.51 [0.46–0.57]) (Fig. 1 and Appendix Results S8 and S9). A reduction in the risk of developing asthma was also consistently observed for both male and female patients and for the different allergen subgroups analysed, in particular for HDM (HR [95% CI]: 0.63 [0.61–0.65]), grass (0.56 [0.53–0.58]), birch (0.45 [0.41–0.50]) and ragweed (0.52 [0.45–0.60]); (Fig. 1 and Appendix Results S4).

Population without asthma at index date: prevention of asthma onset

Specifically looking at the patients without a history of asthma (n = 313,444) with 77,897 exposed to SLIT-liquid and 235,547 controls, exposure to SLIT was found to be associated with a one-third reduction in incident asthma compared with symptomatic AR medication (HR [95% CI] for combined definition: 0.62 [0.60–0.63]; sensitive definition: 0.77 [0.76–0.78]; and specific definition: 0.67 [0.61–0.72]; Table 2 and Fig. 2). The associations were consistent across age, sex and allergen groups, with notably a one-third reduction in patients aged 5–24 years old (combined definition: 0.67 [0.62–0.71]) and a 40% reduction for HDM and grass (combined definition: 0.58 [0.55–0.61] and 0.52 [0.49–0.56], respectively; Fig. 2 and Appendix Results S5, S8, and S9). Some subgroups were not interpretable due to an insufficient number of events (less than 100 events).

Characteristics *n (%)*	Overall population		Pre-existing asthma	
	SLIT Exposed n = 112,492	Controls n = 333,082	SLIT Exposed n = 34,595	Controls n = 97,535
Age at index date years				
Mean (SD)	38 (10.3)	39 (20.9)	37 (10.6)	36 (20.9)
[5–24]	11,435 (10.2)	92,837 (27.9)	4077 (11.8)	33,002 (33.8)
[25–39]	53,349 (47.4)	76,904 (23.1)	17,653 (51.0)	21,772 (22.3)
[40–49]	34,417 (30.6)	55,863 (16.8)	8964 (25.9)	15,825 (16.2)
≥50	13,291 (11.8)	107,478 (32.3)	3901 (11.3)	26,936 (27.6)
Sex				
Male	49,450 (44.0)	132,845 (39.9)	14,031 (40.6)	39,112 (40.1)
Female	63,042 (56.0)	200,237 (60.1)	20,564 (59.4)	58,423 (59.9)
CMUc	5930 (5.3)	44,324 (13.3)	2063 (6.0)	14,667 (15.0)
Comorbidities				
Mild-to-moderate asthma	34,595 (30.8)	97,535 (29.3)	34,595 (100.0)	97,535 (100.0)
Anxiety	7521 (6.7)	47,317 (14.2)	2753 (8.0)	14,048 (14.4)
Depression	7792 (6.9)	36,743 (11.0)	2604 (7.5)	10,815 (11.1)
Morbid obesity	899 (0.8)	5058 (1.5)	343 (1.0)	1933 (2.0)
Nasal polyposis	24 (0.0)	126 (0.0)	11 (0.0)	49 (0.1)
Gastroesophageal reflux disease	9256 (8.2)	56,890 (17.1)	3584 (10.4)	17,834 (18.3)
Sinusitis	293 (0.3)	848 (0.3)	107 (0.3)	242 (0.2)
AR treatment dispensation during the 2 years preceding the index date, mean (SD)				
AH	3.9 (4.7)	5.2 (6.4)	5.2 (5.06)	5.8 (6.43)
INCS	2.3 (2.9)	3.6 (4.4)	2.9 (3.10)	3.8 (4.33)
Co-dispensing AH and INCS	1.5 (2.3)	1.7 (3.5)	1.9 (2.49)	1.8 (3.37)
GINA baseline step				
Step 1 baseline	–	–	12,681 (36.7)	36,865 (37.8)
Step 2 baseline	–	–	4643 (13.4)	11,760 (12.1)
Step 3/4 baseline	–	–	14,824 (42.9)	43,691 (44.8)
Step 5 baseline	–	–	2447 (7.1)	5219 (5.4)
At least one clinician consultation during the 2 years preceding the index date				
Pneumologist	9912 (8.8)	9181 (2.8)	3952 (11.4)	4627 (4.7)
Paediatrician	1073 (1.0)	14,967 (4.5)	358 (1.0)	5890 (6.0)
Death	354 (0.3)	8150 (2.4)	86 (0.2)	2147 (2.2)
Allergens (monoallergy)				
House dust mite	36,765 (32.7)	–	11,148 (32.2)	–
Grass	15,797 (14.0)	–	4089 (11.8)	–
Birch	2840 (2.5)	–	1096 (3.2)	–
Cat	1902 (1.7)	–	933 (2.7)	–
Ragweed	1408 (1.3)	–	385 (1.1)	–
Alternaria	557 (0.5)	–	155 (0.4)	–

AR: allergic rhinitis; CMUc: *couverture maladie universelle complémentaire*; AH: antihistamines; INCS: intranasal corticosteroids; SD: standard deviation.

Table 1: **Description of the population at baseline, before weighting.**

Population with asthma at index date: prevention of asthma worsening–time-to-first asthma treatment step-up

Of the 132,130 patients with a history of asthma at index date, 34,595 were exposed to SLIT-liquid and 97,535 were considered controls. Exposure to SLIT was found to be associated with a one-third reduction in incident asthma compared with symptomatic AR medication (HR [95% CI] for combined definition: 0.62 [0.61–0.63]) with consistent results among all subgroups (Table 2 and Appendix Results S6, and S8, and S9).

In patients treated with SLIT-liquid, the crude incidence of GINA treatment step-up was 13.23 and 13.27 per 100 person-years for patients with baseline step 1 or step 2, respectively, and 2.27 per 100 person-years for patients with baseline step 3/4 (Table 2). Exposure to SLIT was associated with a one-third reduction in GINA step-up (asthma aggravation; HR [95% CI] for baseline step 1: 0.72 [0.69–0.75], baseline step 2: 0.73 [0.68–0.79], and baseline step 3/4: 0.71 [0.65–0.78], respectively; Fig. 3 and Table 2). Associations between SLIT-liquid exposure and GINA step-up were consistent across

	SLIT Exposed			Controls			Crude incidence rate ratio	Adjusted HR
	Person-years (P–Y)	n events/n patients	Crude incidence (%P–Y)	Person-years (P–Y)	n events/n patients	Crude incidence (%P–Y)	[95% CI]	[95% CI]
Sensitive definition								
Overall	448,799	62,579/112,492	13.94	1,262,759	219,044/333,082	17.35	0.80 [0.80–0.81]	0.76 [0.75–0.76]
No pre-existing asthma	382,115	33,169/77,897	8.68	1,106,369	130,714/235,547	11.81	0.73 [0.73–0.74]	0.77 [0.76–0.78]
Pre-existing asthma	66,684	29,410/34,595	44.10	156,390	88,330/97,535	56.48	0.78 [0.77–0.79]	0.71 [0.70–0.72]
Specific definition								
Overall	767,020	2120/112,492	0.28	2,537,074	11,775/333,082	0.46	0.60 [0.57–0.62]	0.66 [0.63–0.69]
No pre-existing asthma	535,687	526/77,897	0.10	1,811,690	3450/235,547	0.19	0.52 [0.47–0.57]	0.67 [0.61–0.72]
Pre-existing asthma	231,333	1594/34,595	0.69	725,384	8325/97,535	1.15	0.60 [0.57–0.63]	0.62 [0.59–0.65]
Combined definition								
Overall	693,887	16,369/112,492	2.36	2,148,691	77,201/333,082	3.59	0.66 [0.65–0.67]	0.64 [0.63–0.65]
No pre-existing asthma	516,481	4915/77,897	0.95	1,665,074	31,863/235,547	1.91	0.50 [0.48–0.51]	0.62 [0.60–0.63]
Pre-existing asthma	177,406	11,454/34,595	6.46	483,617	45,338/97,535	9.37	0.69 [0.67–0.70]	0.62 [0.61–0.63]
GINA step-up (pre-existing asthma)								
Step 1 baseline	52,910	6998/12,681	13.23	142,791	24,872/36,865	17.42	0.76 [0.74–0.78]	0.72 [0.69–0.75]
Step 2 baseline	19,487	2585/4643	13.27	47,724	7664/11,760	16.06	0.83 [0.79–0.86]	0.73 [0.68–0.79]
Step 3/4 baseline	92,576	2101/14,824	2.27	295,773	8928/43,691	3.02	0.75 [0.72–0.79]	0.71 [0.65–0.78]

CI: confidence interval; HR: hazard ratio; P–Y: person-years; SLIT: sublingual immunotherapy.

Table 2: **Associations between exposure to SLIT-liquid and asthma events in overall population and in subgroups without or with asthma.**

age, sex, and allergen groups (Fig. 3 and Appendix Results S7–S9). Some subgroups were not interpretable due to an insufficient number of events (less than 100 events).

Population with asthma at index date: time-to-first asthma treatment step-down

In patients treated with SLIT-liquid, the exposure to SLIT was associated with about 50% of stepping down asthma treatment across the nine years of follow-up (first year OR [95% CI] for baseline step 2: 1.53 [1.42–1.65], baseline step 3: 1.45 [1.39–1.51], and baseline step 4: 1.52 [1.35–1.71], Appendix Results S10).

Discussion

To our knowledge, the EfficAPSI cohort is the largest cohort of patients with treated AR with or without asthma including patients receiving personalised SLIT-liquid. In this nationwide population-based study, treatment with SLIT-liquid was associated with a one-third reduction in the incidence of new asthma events in patients with or without a history of asthma. In patients with pre-existing asthma, the results showed a reduced risk of asthma worsening as demonstrated by a lower incidence of asthma treatment step-up for the SLIT group, regardless of baseline treatment step.

Overall, our study found a 36% reduction in the risk of new asthma event in patients treated with SLIT-liquid compared with patients using symptomatic AR medications alone (controls), according to an outcome definition that is both sensitive and specific. This risk reduction was confirmed using two additional definitions: the first not taking into account medications (specific definition) and the second taking into account major asthma medications (sensitive definition). Our findings further determined in different age and allergen categories confirm and complete the evidence of SLIT effectiveness in reducing the risk of asthma previously established in RCTs and real-world studies (RWSs).[10–25] Of note, our results showed a greater reduction in younger patients which highlights the interest of starting AIT as early as possible.

In patients without pre-existing asthma, treatment with SLIT-liquid could prevent up to 38% of new asthma diagnosis across all age groups and allergen types. These results are in agreement with those from the previously published BREATH program including retrospective, observational, drug dispensing database studies in Germany and France, which consistently found that the risk of new asthma onset was significantly lower in non-asthmatic AR patients treated with SLIT compared to patients receiving symptomatic medications alone (odds ratio 0.70, $p = 0.002$ and 0.56, $p < 0.0001$ for grass pollen SLIT-tablet and 0.69, $p = 0.006$ for birch pollen SLIT-liquid, over the treatment and follow-up periods).[18–21] Similarly, in a previous RWS using a German Health Insurance database, the risk of incident asthma was found significantly lower in a smaller cohort (n = 2431) of AR patients exposed to AIT (SCIT in about 80%, SLIT liquid and tablets for the remaining).[17] A 40% risk

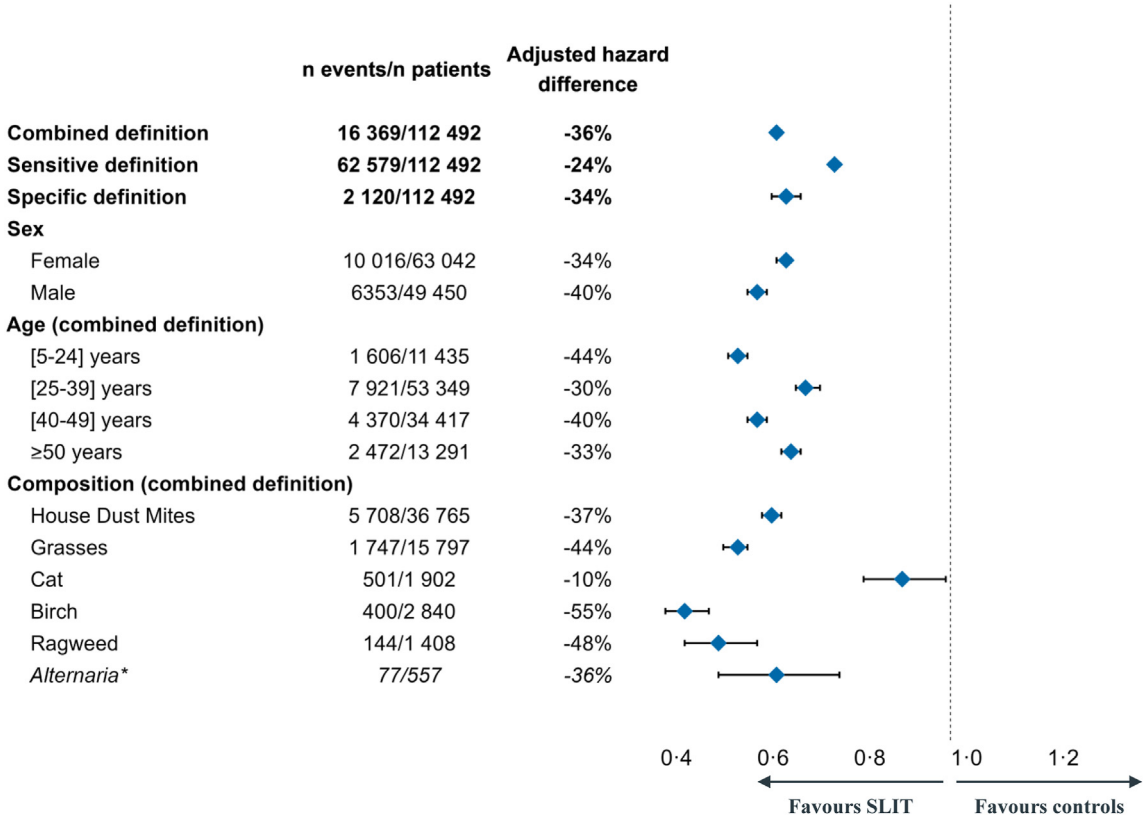

***Fig. 1:* Associations between exposure to SLIT-liquid and asthma events in overall population.** HR: hazard ratio; 95% CI: 95% confidence interval; SLIT: sublingual immunotherapy. *Results lacking statistical power should be interpreted with caution. All stratified results for sensitive and specific definitions are available in Appendix Results S4.

reduction was found for AIT in general, 43% for SCIT and 57% for SLIT-liquid but reaching no statistical significance for the latter subgroup, likely due to the low number of cases.[17] Of note, a trend toward the prevention of asthma development with SCIT using some natural and/or modified allergens could be observed in Wahn et al. and Schmitt et al. studies without statistical significance.[17,21] On another hand, opposite results were found in the retrospective, observational, German database study REACT, using a similar methodology to EfficAPSI with more or less differences, and several routes of administration (mainly SCIT plus SLIT liquid and tablets), allergens, and manufacturers for AIT.[24] In that study, there was a 22% increase in new asthma onset in patients with no history of mild-to-moderate asthma (HR [95% CI]: 1.22 [1.12–1.32]). Fritzsching et al. argued the use of different methodologies and definitions as well as confounding factors may explain discrepancies between studies.[24] Noteworthy, in contrast to previous studies, the EfficAPSI study used definitions either more sensitive by including dispensation of LABA, xanthine or leukotriene antagonists (sensitive definition) or more specific by requiring at least three dispensations of ICS combined or not with LABA or at least one dispensation of omalizumab (combined definition) instead of two dispensed prescriptions of SABA, ICS or combination of ICS/LABA. Moreover, all definitions were not solely based on dispensed medications (not necessarily used or potentially prescribed for other diseases) but included hospitalisations and LTD for asthma ensuring the robustness of our findings. The consistency of results across the three definitions confirms that personalised SLIT-liquid may have an important impact on the onset of asthma in this specific population of AR patients.

In patients with pre-existing asthma, the GINA treatment step analyses confirmed the effectiveness of SLIT-liquid in preventing GINA step-up, regardless of asthma treatment step at baseline. Similarly, a decreased risk of asthma treatment step-up was found in a previous German RWS in patients receiving AIT (not otherwise specified; HR 0.87, 95% CI [0.80; 0.95] from step 1 to step 3) and in REACT study (0.91, 95% CI [0.87; 0.95]), but with a smaller effect.[23,24] Unlike REACT, the EfficAPSI study also found an increased probability of GINA step-down, about 50% depending

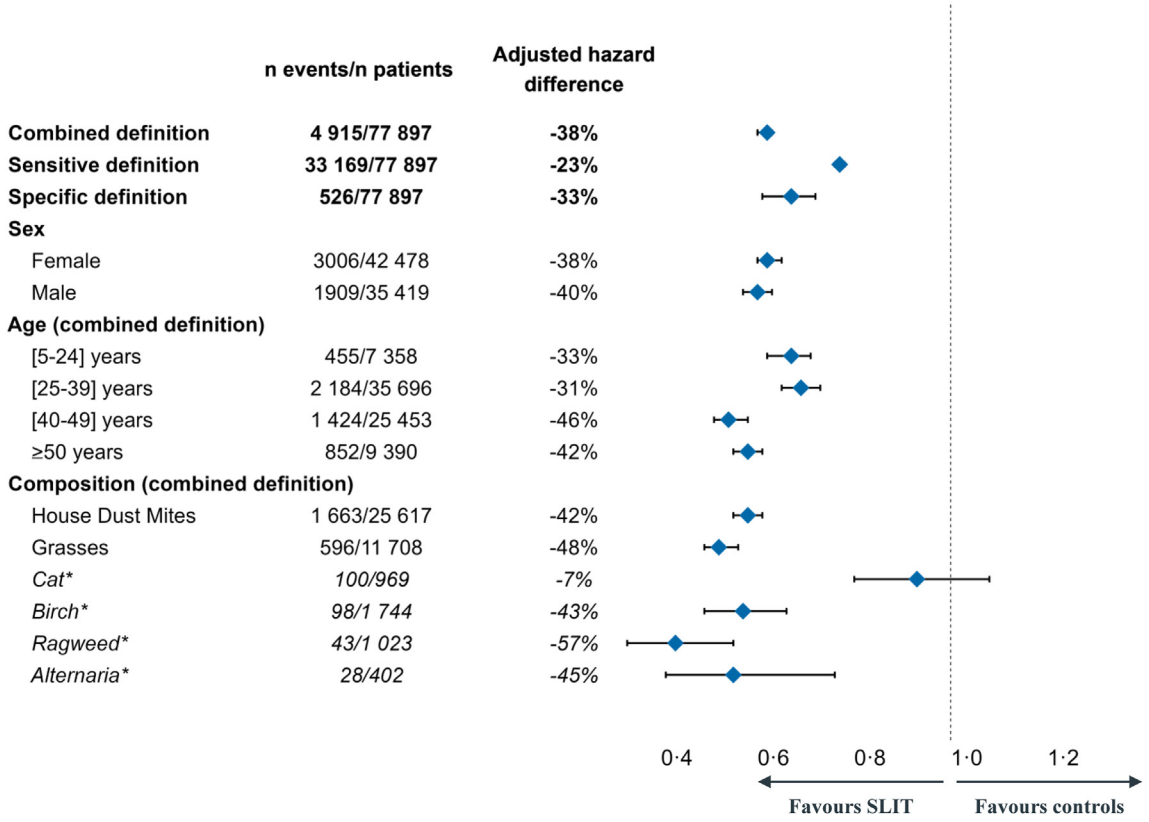

***Fig. 2:* Associations between exposure to SLIT-liquid and asthma onset in patients with no pre-existing asthma.** HR: hazard ratio; 95% CI: 95% confidence interval; SLIT: sublingual immunotherapy. *Results lacking statistical power should be interpreted with caution. All stratified results for sensitive and specific definitions are available in Appendix Results S5.

on GINA baseline step and year of follow-up. In the BREATH studies, the progression of asthma was reduced to about 20%–40% in patients treated with SLIT (liquid or tablets) and in a similar range with birch pollen SCIT (natural or modified), compared with patients treated with symptomatic treatments alone.[18–21] It has been reported that healthcare use and inherent costs increased with the GINA steps to control asthma, and yet quality of life decreased.[30,31] In the French CONSTANCES cohort, linked to the SNDS, reimbursed drug costs were twice as high for steps 3 or 4 compared with steps 1 or 2 and nine times as high for step 5.[31] In our study, treatment with SLIT-liquid prevented up to 29% of stepping-up in patients with baseline GINA treatment step 1, 2 or 3/4, suggesting substantial cost savings besides an improved quality of life for the patients.

The EfficAPSI cohort was based on the real-world French nationwide database linked to the Stallergenes Greer dispensing registry. Compared with REACT patients, EfficAPSI patients were older (mean age of 38 years *vs.* 29.5 years), more often women (almost 60% *vs.* 47%), and were dispensed more AH or INCS per year before initiating AIT (mean about one to two per year *vs.* 0.5 per year). On the other hand, both cohorts included one third of patients with allergic asthma. The older population could be impacted by the suboptimal linkage of children (only 0.7% for exposed *vs.* 20.7% for controls), inherent to the French national system based on two generic identifiers for reimbursement (children one and parents one). Noteworthy, the baseline characteristics of EfficAPSI patients were consistent with the previously published epidemiological data of French allergic patients.[1,32] Since the EfficAPSI cohort was representative of the French treated AR population, the results could be extrapolated to the French population. As with other observational studies based on medico-administrative database, the EfficAPSI study may suffer from the influence of unmeasured confounders (*e.g.*, smoking, air pollution or lifestyle, socio-economic status, over the counter medicines, dispensed but not taken drugs, AR severity/control, allergen sensitisation profile). To compensate as much as possible for this gap, we used the IPTW, a robust propensity-score method designed to address confounding by indication in RWSs and aiming to achieve a balanced distribution of confounders across treatment groups.[33] To enhance the

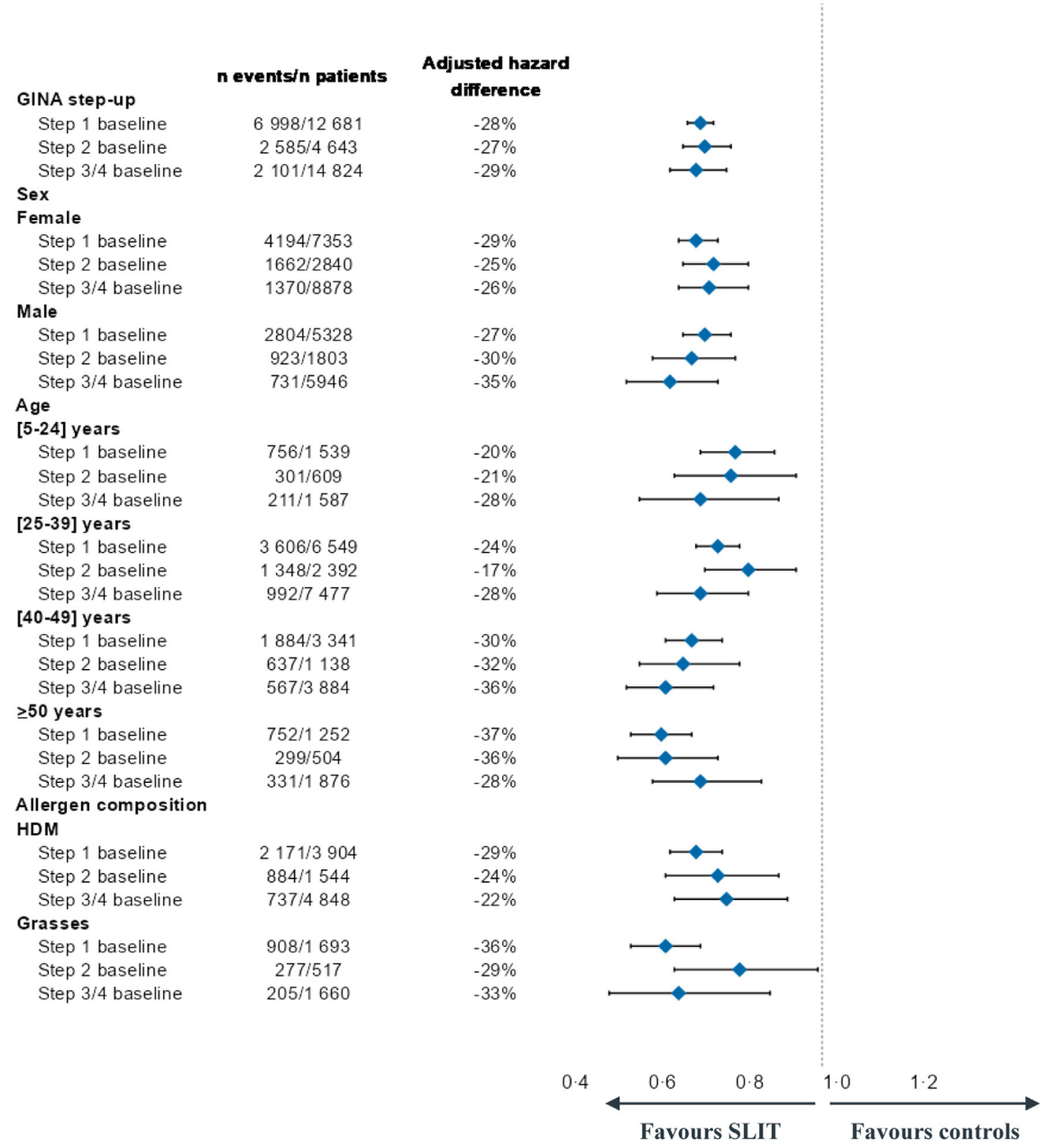

***Fig. 3:* Associations between exposure to SLIT-liquid and GINA treatment step-up in patients with pre-existing asthma.** HR: hazard ratio; 95% CI: 95% confidence interval; SLIT: sublingual immunotherapy. *Results lacking statistical power should be interpreted with caution.

comparability of patients among allergens stratifications, month of the index date and the department of residence (illustrating the pollen presence) were particularly taken into account. The limited deviation from the proportional hazard assumption had no impact on the results, so no correction was applied to the model. Finally, several definitions and sensitivity analyses were performed to reinforce the consistency and robustness of the initial analyses: sensitive (based on drug dispensation) and specific (based on hospitalisation) definitions to challenge the combined definition based on specific drugs and hospitalisation and the impact on the GINA treatment step. Besides, this intention-to-treat design included all patients treated with SLIT-liquid, whether they were adherent or not, suggesting the observed positive effect may be underestimated. It is worth to acknowledge that the patients dispensed SLIT-liquid may have experienced a "placebo effect" due to

positive expectations raised by a treatment offering new perspectives when they were inadequately treated with symptomatic medications. Nevertheless, compared to patients only dispensed symptomatic treatment, the substantial risk reduction of asthma events consistently demonstrated throughout the analyses remains in favour of SLIT.

In contrast to REACT, which evaluated several routes of administration, mainly SCIT in the German market, the EfficAPSI cohort only evaluated a SLIT-liquid. This formulation offers the advantages of flexible composition, protocols and dosing that can be adapted to each patient according to their profile and or condition as observed in a French retrospective study.[27] Precision dosing and personalised medicine are becoming more commonplace in clinical practice, particularly in cancer and immunologic diseases. AR and in particular asthma are public health concerns, with a significant impact on quality of life, and the identification of the responsible allergens allows the adaptation and the treatment of patients against all their identified allergies. Precision dosing of the SLIT-liquid could optimise the overall risk–benefit profile of AIT for each patient throughout the course of treatment, making it possible to reach both short- and long-term efficacy while maximizing safety.

Conclusion

In this national real-world study with the largest number of person-years of follow-up to date in the field of AIT, SLIT-liquid was associated with a significant reduction in the risk of asthma events. Multiple stratification confirmed the effectiveness of SLIT-liquid in preventing asthma or reducing the risk of an asthma worsening, for all ages and allergens evaluated. The evaluation of three event definitions, more or less sensitive and specific, and of the GINA treatment step evolution reinforced the rigorous methodology of the EfficAPSI study to provide important insights about SLIT-liquid as personalised medicine. This and the completeness of the data with on- and post-treatment follow-up allow a more robust and consistent evaluation of SLIT-liquid in real-life to substantiate its evidence as a relevant causal treatment option for patients with respiratory allergies, with abilities to prevent disease progression.

Contributors

All authors were involved in the conception and design of the study and interpretation of data. Amandine Gouverneur, Jade Vadel and Cédric Collin were involved in the analyses and in drafting the manuscript or revising it critically for intellectual content. All authors approved the final version of the manuscript; and all authors are agreeing to be accountable for all aspects of the work.

Data sharing statement

According to the principles of data protection and French regulations, the authors cannot publicly release the data from the "*Système National des Données de Santé*" (SNDS). However, any person or structure, public or private, for-profit or nonprofit can access SNDS data upon authorization from the "*Commission Nationale de l'Informatique et des Libertés*" (*i.e.*, the French Data Protection Office) to carry out a study, research, or an evaluation of public interest (https://www.snds.gouv.fr).

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2024.100915.

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