Allergen immunotherapy: what is the added value of real-world evidence from retrospective claims database studies?

Philippe Devillier, Pascal Demoly, Mathieu Molimard

Taylor & Francis
Taylor & Francis Group

Expert Review of Respiratory Medicine

ISSN: 1747-6348 (Print) 1747-6356 (Online) Journal homepage: https://www.tandfonline.com/loi/ierx20

Allergen immunotherapy: what is the added value of real-world evidence from retrospective claims database studies?

Philippe Devillier, Pascal Demoly & Mathieu Molimard

To cite this article: Philippe Devillier, Pascal Demoly & Mathieu Molimard (2020): Allergen immunotherapy: what is the added value of real-world evidence from retrospective claims database studies?, Expert Review of Respiratory Medicine, DOI: 10.1080/17476348.2020.1733417

To link to this article: https://doi.org/10.1080/17476348.2020.1733417

Published online: 04 Mar 2020.

EXPERT REVIEW OF RESPIRATORY MEDICINE
https://doi.org/10.1080/17476348.2020.1733417

Taylor & Francis
Taylor & Francis Group

PERSPECTIVE

Allergen immunotherapy: what is the added value of real-world evidence from retrospective claims database studies?

Philippe Devillier [a], Pascal Demoly [b] and Mathieu Molimard [c]

[a]UPRES EA 220, Department of Airway Diseases, Hôpital Foch, University of Versailles Saint Quentin, University Paris-Saclay, Suresnes, France; [b]Department of Pulmonology, Division of Allergy, Hôpital Arnaud De Villeneuve, University Hospital of Montpellier, Montpellier, France and Equipe EPAR – IPLESP, Sorbonne Université, Paris, France; [c]Pharmacology Department, University of Bordeaux, INSERM Unit CR1219, Bordeaux, France

ABSTRACT

Introduction: Randomized controlled trials (RCTs) show that allergen immunotherapy (AIT) has proven long-term efficacy in patients with allergic rhinitis (AR). However, RCTs have limited generalizability and there is growing recognition that real-world evidence (RWE) is necessary to provide complementary data to those of RCTs, and corroborate their findings. Until recently, data from the real-world setting investigating the benefits of AIT for the treatment of patients with grass and birch pollen-associated AR were sparse, but new retrospective claims database studies from France and Germany have confirmed the sustained benefits of grass and birch pollen AIT in terms of significantly reduced progression of AR and asthma, and a significantly decreased risk of new-onset asthma.

Areas covered: Here, we review the value of RWE used alongside data from traditional RCTs, and its potential strengths and limitations, and summarize the findings of the recent RWE studies investigating the benefits of AIT for the management of patients with grass and birch pollen-associated AR.

Expert opinion: There is growing recognition of the necessity and value of RWE as a complement to data acquired in RCTs, to better understand the effects of AIT treatments in a broader, more representative patient population, and to help guide clinical decision-making.

ARTICLE HISTORY
Received 19 December 2019
Accepted 19 February 2020

KEYWORDS
Allergen immunotherapy; allergic rhinitis; asthma

1. Introduction

Allergen immunotherapy (AIT) in the form of subcutaneous or sublingual immunotherapy (SCIT and SLIT, respectively) is the only disease-modifying treatment available for allergic rhinitis (AR) with proven long-term efficacy [1]. AIT reduces the risk of asthma in patients with AR by inducing allergen-specific immune tolerance, and may also prevent the development of new allergen sensitizations, although further studies are needed to confirm this latter observation [2]. AIT is recommended in European guidelines for use in conjunction with patient education, specific allergen avoidance and symptomatic pharmacotherapy [3].

With a growing recognition of the potentially limited generalizability of randomized controlled trials (RCTs) to clinical practice [4], there is a need to demonstrate the long-term effectiveness and preventive effects of AIT in a real-world setting [5]. Here, we discuss the value of real-world evidence (RWE) and examine the current evidence base for AIT and the opportunities it may offer to improve patient care in routine practice.

2. What challenges do clinicians face when treating patients with AR using AIT in real-life practice?

Clinicians face a number of challenges when treating patients with AIT in daily practice. Among these are the problems of selecting the right patient [6,7] – for example, do we need to consider whether AIT is appropriate for certain patient types or may only be effective in selected patients [8], and how can we be confident that the results from published studies are applicable to patients in our own practice [9]?

3. There is already a convincing body of evidence from RCTs demonstrating the value of AIT as the only disease-modifying therapy for AR. What additional value does RWE provide?

RCTs are considered the gold standard for assessing efficacy and safety, and are a requirement for gaining regulatory approval of a drug. However, many patients in everyday clinical practice do not fit the narrow inclusion and exclusion criteria employed in these trials and show variation in gender, age, ethnicity, lifestyle, comorbidities, disease severity, concomitant medications, and compliance with treatment [10]. Although there is a robust body of evidence from RCTs supporting the efficacy of SLIT/SCIT in patients with AR and asthma, poor adherence and/or other factors may impact on the effects of AIT in clinical practice, as they do for pharmacotherapy of any chronic disease. This has raised concerns that it may be difficult to generalize the results from RCTs to wider patient populations [9]. For example, a study was conducted to find out to what extent a 'real-life' patient population with obstructive lung disease could fit into selection criteria for asthma that are commonly used in clinical research trials

CONTACT Philippe Devillier p.devillier@hopital-foch.org UPRES EA 220, Department of Airway Diseases, Hôpital Foch, University of Versailles Saint Quentin, University Paris-Saclay, Suresnes, France

Article highlights

- Allergen immunotherapy (AIT) has proven long-term, disease-modifying efficacy in patients with allergic rhinitis (AR), can reduce the risk of new-onset asthma in these individuals, and may also prevent the development of new allergen sensitizations.
- Real-world evidence (RWE) of AIT complements the findings of randomized controlled trials (RCTs), and there is growing recognition among health-care providers and regulatory bodies of the valuable contribution it can make to clinical decision-making.
- RWE studies have several advantages over RCTs, including a broad, real-life clinical practice patient population, greater generalizability, and the ability to assess clinical endpoints that may be underpowered in RCTs.
- However, RWE studies have inherent risks of bias mainly due to the use of proxies (i.e. dispensing data for AR and asthma reimbursed medications) to ascertain clinical information. Matching procedures can minimize confounding bias, but not all of the other types of bias.
- Recent RWE studies in patients with grass and birch pollen allergies have demonstrated that versus standard of care, AIT improves AR symptom control after treatment cessation, as well as asthma control, and decreases the risk of developing asthma.
- RWE studies of AIT in patients with AR and asthma confirm and build on the efficacy findings of RCTs, and their results can be used to guide clinical management and assist counseling of patients, so much so that recent guidance supports the inclusion of RWE data in formulating guideline recommendations.

[absence of significant comorbidities, fixed expiratory volume in 1 s (FEV_1) 50–85% of predicted, historical reversibility of FEV_1 > 12% in the last year, and no history of smoking or smoking burden < 10 pack-years if an ex-smoker]. Only 5.4% of the study participants met these criteria, and when additional criteria were imposed (regular use of inhaled corticosteroids and having symptomatic asthma), the proportion of eligible asthma patients decreased further to just 1.3% of all patients [11]. In a similar study examining how closely patients with AR enrolled in RCTs resemble those seen in primary practice, the same held true (only 7.4% of patients would have been enrolled in the RCTs), although for different reasons to those of the obstructive lung disease study [12]. These findings clearly indicate that RCTs may only include a very small and highly selected fraction of a real-life population of patients with the specific condition of interest.

In contrast, RWE studies better reflect the broad range of patients and the complexity we see in clinical practice [4]. They are able to reveal the interplay between patient characteristics, their preferences, and lifestyle and treatment outcomes in a way that is not possible with RCTs because of their strict inclusion and exclusion criteria [13]. Because of their typically longer duration and more relaxed selection criteria compared with RCTs, RWE studies are better able to explore how such parameters may differ between therapies and can investigate clinical outcomes that may be underpowered in RCTs [13]. Data from these studies have the potential to improve the delivery of medical care, reduce overall costs, and improve patient outcomes [10].

RWE studies may use information from sources such as electronic hospital records, disease registries, and prescription databases, which provide large datasets from diverse patient populations, or may be observational, and collect prospective or retrospective data over a long period of time. They can therefore provide information on the long-term safety and effectiveness of drugs in large heterogeneous populations, together with data on drug utilization patterns and health economic outcomes [14]. In terms of AIT, real-world studies offer the ability to assess evolving risk-benefit profiles, including the effectiveness of AIT beyond 2 years post-treatment and the long-term preventive effects of AIT on asthma progression and new asthma onset [15].

Evidence from RWE studies complements data from RCTs and is increasingly recognized by regulatory bodies as a valuable source of information to support decision-making, monitoring of post-marketing safety and life cycle product development, and to assist clinical trial design [14]. Real-world data form a key component of health-care technology assessments conducted by bodies such as the UK National Institute for Health and Care Excellence (NICE) to guide clinical decision-making and are also increasingly utilized by payers and other key stakeholders to inform decisions regarding formulary placement and the allocation of health-care resources [14].

Recently, several RWE studies have been conducted to evaluate the effect of AIT versus non-AIT therapies on AR progression and asthma in patients with grass or birch pollen-associated AR [5,15–18], using retrospective analyses of data from French and German prescription databases. Taken together, these studies illustrate well the strengths and limitations of such a RWE approach (summarized in Table 1). These databases do not collect clinical information, such as confirmed diagnoses, meaning that the presence and/or progression of AR and asthma must be inferred from prescriptions. During this process, stringent methodology was used to ensure the highest chance of accurately capturing this information; for example, intranasal corticosteroids were selected as a proxy for the diagnosis and treatment of AR, thus eliminating the risk of including patients in the analysis who did not have this condition. Over-the-counter medications are also used as treatments for AR but were not tracked in the prescription databases. However, the majority of intranasal

Table 1. Strengths and limitations of the RWE studies assessing the development and/or progression of AR and/or asthma in patients using AIT [5,15,17,18].

Strengths	Limitations
• Reflects clinical practice and dispensing of AIT • Use of nationwide, representative, large patient cohorts • Permits comparison of AIT versus standard of care • Employs a stringent methodology and design, involving matched control groups to minimize confounding bias • Enables testing of different treatment formulations using the same methodology • Assesses longitudinal data, allowing patient follow-up over time • Data are available across many years, enabling assessment of long-term effectiveness • Demonstrates consistency of findings across countries with differing treatment practices	• Retrospective design • Clinical information must be ascertained via proxies (i.e. dispensing data for AR and asthma medications) • Only reimbursed medications are recorded • Statistical adjustment needed for control group definition

AIT, allergen immunotherapy; AR, allergic rhinitis; RWE, real-world evidence.

corticosteroids delivered in France and Germany are prescribed, which should have minimized any bias. On the other hand, a minority of oral antihistamine medications in Germany are delivered by prescription, which could lead to underestimation of the intensity of AR treatment. However, this potential bias would have affected both the AIT and non-AIT groups equally. As is always the case when claims data are analyzed, the actual use of any medications remained unknown; instead, only dispensing data were available, and information such as the quality of use of inhaler devices for asthma or actual use by the patient, was not available. Therefore, non-persistence /adherence with treatment could have been subject to over- or underestimation. However, the claims data in these studies provide information on actual dispensing of therapies by community pharmacies, and this represents a major advantage, because these data more closely approximate real-life use than prescribing data are able to.

Differences in symptom and disease severity between treatment groups may manifest because of the presence of masked residual confounders. As is often the case with claims data analyses, the RWE studies had no access to clinical, biological or lung function measurements, which are pivotal to the assessment of AR and/or asthma severity, and sensitization status. As a means of evaluating patient outcomes with either AIT or non-AIT therapy use in as comparable a fashion as possible, matching was undertaken in the RWE studies. Matching by index year avoided any confounding bias due to differences in the length and/or intensity of successive grass and birch pollen seasons over the analysis period. Other possible confounders included patient sex, age at index date, main prescriber, asthma status at index date, AR severity before index date, and duration of AIT use, and while these were not employed as matching criteria, they were subsequently corrected for in all analyses by multiple regression. Although the matching strategy minimized confounding bias due to differences in demographics or baseline characteristics in patients in either treatment cohort, it also reduced the size of the study population, with a possible impact on the statistical power of comparisons.

The outstanding and most important strength of these studies was their use of real-world data from a broad population that is more representative and generalizable than data from RCTs. These RWE studies were based on a large patient sample in two major European countries, enabling a comparison of AIT to be made versus standard of care, and to assess pragmatic endpoints reflecting a long-term benefit of treatment. Importantly, the RWE studies demonstrated consistent findings on the effect of AIT on AR and asthma in this patient population, despite using data from two countries that have slightly differing prescribing practices and approaches to treatment.

4. What does the evidence from RWE studies of AIT show?

The RWE base on the benefits of AIT is growing. Recent RWE studies have demonstrated that AIT positively impacts on AR control after treatment cessation as well as asthma development and control in patients with grass pollen and birch pollen allergies, compared to the standard of care (SoC) (i.e. symptomatic drug treatments for AR and/or allergic asthma treatments). Importantly, these studies are part of the first efforts to develop a substantial RWE base around AIT and demonstrate insights into its effects.

Taking a closer look at the findings from these recent studies, a retrospective, longitudinal analysis of prescription records, collected between 2012 and 2016 in the French IMS Lifelink™ Treatment Dynamics database, was conducted [15]. Patients were included with moderate-to-severe AR in three successive pollen seasons (including the season before the index date), and for patients in the SLIT group, ≥ 1 year of follow-up after the last dispensed prescription of SLIT tablets. Patients with severe asthma (defined as (i) having ≥ 1 prescription of omalizumab or (ii) having ≥ 2 prescriptions of oral corticosteroids recorded outside the pollen season in patients receiving a combination of an inhaled corticosteroid [ICS] and a long-acting β2-agonist [LABA]) during the pre-index period were excluded. For most of the time period selected for analysis of the IMS Lifelink™ database (2012–16), only omalizumab was approved in France for the treatment of severe asthma, and therefore this was the only biologic listed as an exclusion criterion in the study protocol. Patients (n = 1,099) who had received ≥ 2 successive seasonal treatment cycles with grass pollen SLIT tablets were compared with control patients (n = 27,475) who had received symptomatic medications only. Patients were matched for index year (primary analysis) and additionally age (secondary analysis). The primary endpoint was change over time in number of symptomatic AR medication prescriptions during follow-up. Secondary endpoints included time to new asthma onset (i.e. incident asthma, defined as ≥ 2 dispensed prescriptions of asthma medication in the same year or in two successive calendar years, during the treatment and follow-up periods in patients who were untreated for asthma during the pre-index period) and change over time in the number of dispensed prescriptions for asthma medication during the treatment period and during the follow-up period in patients with AR and asthma at the index date (Figure 1).

For symptomatic AR medication prescriptions, the SLIT group was associated with a 50% decrease in the pre-index /follow-up ratio; in contrast, 20% and 30% increases were seen in the control group with or without age matching, respectively (both $p < 0.0001$ *vs* SLIT). During the follow-up period, 11 (1.8%) patients in the SLIT group and 782 (5.3%) patients in the control group started asthma treatment. Compared with controls, the SLIT group had a significantly lower relative risk of medication dispensing for new asthma (by 63.7% [95% confidence interval (CI): 31.5%; 80.7%] or 62.5% [95% CI: 29.1%; 80.1%] with ($p = 0.0018$) or without ($p = 0.0025$) age matching, respectively). Patients in the SLIT group also had a slower progression of asthma medication dispensing during follow-up versus controls (regression coefficient: −0.61 [−0.76; −0.46] with age matching and −0.58 [−0.74; −0.42] without age matching; both $p < 0.0001$).

A large-scale, retrospective, RWE analysis of the longitudinal German IQVIA HealthLRx prescription database followed patients for up to 6 years after treatment cessation [18]. Data were analyzed between 2008 and 2016. Patients were included who had ≥ 1 prescription of intranasal corticosteroids in the year prior to the index date; and ≥ 2 years of follow-up

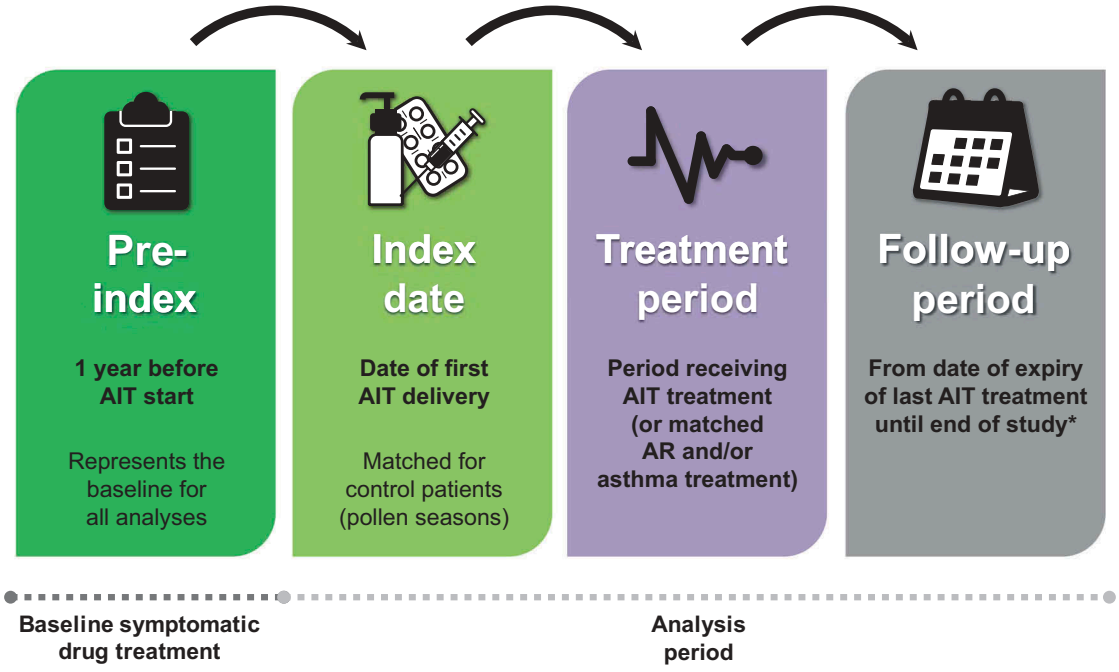

Figure 1. Key study periods examined in the retrospective, longitudinal, real-world analysis of prescription records for grass pollen-associated allergic rhinitis and asthma from the IMS Lifelink™ Treatment Dynamics database [15].

*At ≥ 1 year of follow-up after AIT cessation. AIT, allergen immunotherapy; AR, allergic rhinitis.

after the expiry of the last SLIT tablet prescription. Patients with severe asthma (defined as having ≥ 1 prescription of omalizumab), perennial asthma (defined as having ≥ 3 prescriptions of ICS, ICS/LABA combinations or depot formulations), or methylxanthine use over three successive 4-month periods (January–April, May–August, and September–December) before or during the year of the index date were excluded. A total of 2,851 patients who had received ≥ 2 successive seasonal treatment cycles with grass pollen SLIT tablets were identified. These were compared with 71,275 control patients who had seasonal AR and had been prescribed nasal steroids during the grass pollen season but had not received AIT treatment, matched for treatment index year. The primary endpoint of the study was change over time in AR symptomatic medication prescriptions after stopping treatment. Secondary endpoints were new asthma onset (defined as time to first prescription of short-acting β-agonists (SABAs) or ICS, during and after stopping treatment, in patients without asthma at index date) and change over time in asthma medication prescriptions in patients with asthma at index date, during treatment and follow-up.

After treatment cessation, AR medication use was 18.8% lower (after covariate adjustment and relative to the pre-treatment period) in the SLIT tablet group than the non-AIT group ($p < 0.001$), asthma onset was less frequent (odds ratio [OR]: 0.696; $p = 0.002$), and time to asthma was significantly longer (hazard ratio [HR]: 0.523; $p = 0.003$). During the follow-up period, 45 (21.6%) and 2579 (41.5%) patients initiated asthma treatment in the SLIT and control groups, respectively. After SLIT cessation, asthma medication use fell by an additional 16.7% (relative to the pre-treatment period) in the SLIT tablet group versus the non-AIT group ($p = 0.004$) [18].

A subanalysis of the IQVIA HealthLRx prescription database of patients with AR receiving 5- or 1-grass pollen SLIT tablets (n = 1,466/1,385) versus patients not using AIT who received symptomatic treatment only (n = 71,275) has also been conducted [5]. Among patients receiving either SLIT tablet, the mean number of prescriptions for AR medications was significantly decreased during up to 6 years of follow-up versus the non-AIT group ($p < 0.001$). Over the full-analysis period, 8.8% (OR: 0.676, $p = 0.011$), 10.3% (OR: 0.720, $p = 0.060$), and 11.6% of patients in the 5- and 1-grass pollen SLIT tablet and non-AIT groups, respectively, developed new-onset asthma. For all treatment-analysis periods, both SLIT tablet groups were associated with fewer prescriptions for asthma medications than the non-AIT control group.

A second retrospective analysis of the IQVIA HealthLRx prescription database evaluated the effect of 6 AITs (natural pollen SLIT/SCIT, 4 allergoid SCITs) versus symptomatic medication use in patients with birch family pollen-associated AR and/or allergic asthma from 2009 to 2017 [17]. Inclusion criteria were ≥ 1 defining prescription for AR symptomatic medication (nasal corticosteroids, oral/systemic antihistamines) in the year prior to index date and/or ≥ 2 defining prescriptions for asthma medications [ICS, ICS/LABA, short-acting beta agonists] in the birch family pollen seasonal cycle defined by index season or the prior season; and ≥ 2 years of follow-up post-treatment end. Exclusion criteria were severe asthma (defined as receiving prescriptions for benralizumab, dupilumab, mepolizumab, omalizumab, or reslizumab) or perennial asthma (defined as having ≥ 3 prescriptions for ICS or methylxanthines, over three successive 4-month periods before or during the pollen seasonal cycle of the index date) without exacerbations during the season. AIT patients (n = 9001) had

completed at least 2 successive seasonal treatment cycles, while non-AIT patients (n = 45,005) had received at least 3 AR prescriptions over three seasons or during the prior month. Patient matching was by age, index year, sex, main indication at index, number of seasonal cycles within the treatment period, and number of prescriptions for AR/asthma treatments at baseline. Study endpoints were stratified by overall AIT versus non-AIT groups (primary analyses), and the six individual AIT product subgroups versus non-AIT control group (secondary analyses), and included AR progression from 2 to 6 years after stopping active treatment in patients with AR, with or without asthma, at baseline; development and time to development of asthma in patients with AR, but not asthma, at baseline, on-treatment and from 2 to 6 years post treatment; and asthma progression from 2 to 6 years after stopping active treatment in patients with asthma, with or without AR, at baseline.

At up to 6 years of follow-up, significantly more patients in the AIT group (65.4%) were AR medication-free than in the non-AIT group (47.4%) (OR [95% CI]: 0.51 [0.48–0.54]; $p < 0.001$, 28.6% covariate-adjusted reduction *vs* non-AIT; $p < 0.001$), and significantly more patients in the AIT group (49.1%) were asthma medication-free than in the non-AIT group (35.1%) (OR [95% CI]: 0.59 [0.55–0.65]; $p < 0.001$, 32% reduction *vs* non-AIT; $p < 0.001$) or had reduced their existing asthma medication use (32% covariate-adjusted reduction *vs* non-AIT; $p < 0.001$). During treatment, the risk of developing a new case of asthma was significantly reduced in the AIT *vs* non-AIT group (OR: 0.83; $p = 0.001$). The magnitude of benefits was higher for SLIT versus SoC than for other therapeutic options (namely natural SCIT and allergoids) versus SoC.

Taken together, these findings clearly demonstrate the long-term benefits of AIT, which may translate into clinical practice as a slower progression of AR and a preventive effect on asthma (with a reduced risk of new asthma onset in the non-asthmatic population and slower asthma progression in the asthmatic population) in routine use. However, it is important to remember that no diagnoses were recorded in the databases analyzed in these studies, meaning AR and asthma medication use had to serve as a proxy to identify disease; furthermore, it was not possible to capture over-the-counter medication use in these databases.

5. Are there any aspects of these RWE studies that can help us to better understand the similarities and differences in their findings?

The findings from these RWE studies are in line with those generally observed in RCTs of grass and birch pollen SLIT [19–21], and add to the growing body of evidence demonstrating the benefits of AIT.

The French study by Devillier et al. [15] was similar to the one performed by Zielen et al. in Germany [18], but included a broader panel of reimbursed drugs. The degree of long-term relief in AR and the extent of the reduction in asthma onset and progression were apparently greater in the French study. These disparities may have been due to methodological differences between the studies, and/or differences in prescribing habits and reimbursement policy between France and Germany; for example, in Germany, oral antihistamines are reimbursed for pediatric patients, while in France, they are reimbursed for both adult and pediatric patients, which may have led to a lower estimate of the intensity of AR treatment in the German study. There are also some data which suggest that the severity of allergic disease was greater among patients in the French study than the German study. At the index date, the proportions of patients with asthma in the French study (37.6% in the SLIT group and 39.2% in the control group) were higher than in the German study (21.2% in the SLIT group and 21.0% in the control group) [15,18], although the overall incidence of new-onset asthma was lower in France than Germany.

In the German grass pollen study, a sustained beneficial effect of SLIT on lowering new-onset asthma risk was observed in the post-treatment period [18]. In contrast, the German tree pollen study showed a significant reduction in the progression of asthma medication use and a significantly decreased risk of new-onset asthma medication use during AIT treatment; however, a persistent post-treatment effect could not be shown [17]. In the latter study, statistical power to detect an effect on new-onset asthma may have been lowered, due to relatively few patients developing asthma. This study also included a much lower proportion of children in the birch pollen AIT group than the grass pollen SLIT study (~20% versus ~50%, respectively). This is of importance, given that the ability of AIT to prevent asthma appears to be greatest in children [22].

In all grass pollen and birch RWE studies, AR progression was only analyzed for the follow-up period, because as an inclusion criterion, all patients in the non-AIT group had received ≥ 1 AR prescription in the treatment period, whereas the AIT/SLIT group need not have received any; therefore, any comparisons between the two groups for the treatment period were invalidated by the study design. In contrast, the asthma analyses were performed for the treatment, follow-up, and full-analysis periods [5,15,17,18].

In the RWE studies, as observed in the AIT cohort, dispensing of AR medication prescriptions in the non-AIT cohort appears to decrease over time as well, suggesting less of a need for symptomatic rescue medication in this group of patients, compared with earlier years of the study. This can mainly be explained by the aforementioned inclusion criteria for the non-AIT group, which required patients to have moderate-to-severe AR, defined as ≥ 1 dispensed prescriptions of intranasal corticosteroids over 3 consecutive years in the German study [18] or ≥ 2 dispensed prescriptions of intranasal corticosteroids over 2 consecutive years in the French study [15]; these criteria were not necessary for the AIT cohort.

6. There is a convincing body of RWE on pollen AIT. How can we use these data to improve the management of patients in our clinical practice?

RWE is emerging as an important means to better understand the utility of treatment interventions in broader, more representative patient populations [14]. Because RWE studies are performed in actual clinical practice settings, they are better able to assess the effectiveness and safety of medications in the way they are used by patients and clinicians in routine practice [14], and by taking into account the

relationships between patient characteristics, lifestyle factors, treatment compliance and regimens, comorbidities, quality of life, and clinical outcomes. Therefore, RWE can aid patient selection, guide treatment decisions, and instill confidence in prescribing AIT, as well as improve patient communication. Regarding those RWE studies that evaluated the effect of AIT on AR and/or asthma, the reproducibility of findings between the French and German analyses should reassure clinicians regarding the effectiveness of SLIT and SCIT for the management of these conditions, and in delaying or preventing the new onset of asthma.

For seasonal allergens e.g. pollens, AIT is administered perennially or started a few months prior to the pollen season, to allow the treatment to modulate the immune system before the season starts [19,22,23]. Patients are treated based on symptoms experienced in previous seasons; however, the severity of these symptoms may not be an accurate predictor of upcoming symptoms due to various complicating factors [6]. There is also a complex interaction between patient factors (e.g. polysensitization/potential exposure to other allergens, pollutant exposure, allergen avoidance measures, disease progression), allergy triggers (e.g. pollen levels, weather patterns), symptomatology, and the type of AIT [6,23,24].

The majority of patients with AR or allergic asthma we see in clinical practice are polysensitized [25]. AIT has demonstrated efficacy in large clinical trials conducted in primarily polysensitized patients [25,26], and we can be confident that AIT is equally effective in mono- and polysensitized patients if the relevant allergen is selected [19,25,27,28].

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 [5,29]. Evidence from RCTs suggests that more severe disease is associated with a greater magnitude of AIT effect [25,30].

Clinicians can easily use the findings from RWE studies to communicate with their patients and answer their questions with real-world data, rather than findings from patients in a highly selected clinical trial setting. We often find patients lack knowledge about AIT and there are numerous misconceptions about this therapy [25,31]. Furthermore, adherence to AIT is reportedly lower in real-world settings than in clinical trials [32–34], with lack of tolerability, cost, and perceived ineffectiveness being cited as possible factors for decreased adherence [35], so the provision of accurate information regarding adverse effects and when to expect an improvement in symptoms is very important.

Because the quality of systematic reviews of AIT is based on the quality of the included studies, and bearing in mind the high rate of clinical and methodological heterogeneity among studies, the concept of a "class effect" for AIT products is overly simplistic and not justified. Instead, a product-specific evaluation, as suggested by the WAO [36], should be used to support efficacy and claims of sustained and disease-modifying effects, and high-quality data from RWE studies should also be considered in this process [4].

7. Conclusions

RWE is a valuable and necessary complement to data acquired in RCTs, and regulatory bodies are increasingly recognizing the important contribution it can make to clinical decision-making. RWE studies have several advantages over RCTs, including evaluation of a broader patient population that more closely mirrors what is seen in clinical practice, greater generalizability (external validity), and enabling the assessment of long-term safety and effectiveness, as well as clinical endpoints that may be underpowered in RCTs. Findings from recent retrospective studies using RWE have demonstrated the benefits of grass and birch pollen AIT in significantly reducing the progression of AR and asthma, and significantly decreasing the risk of new-onset asthma, thus confirming and extending existing data from RCTs.

8. Expert opinion

In the future, it is likely that the use of precision medicine and the identification of valid biomarkers will help to stratify patients who are eligible for AIT [37]. To date, there are no validated or widely accepted candidate biomarkers to predict or monitor clinical response to AIT [37], although evidence has shown that an elevated ratio of specific immunoglobulin E (IgE) to total IgE ratio is a potential positive predictive marker [24]. Therefore, in the meantime, we are relying on evidence from clinical trials and RWE studies to guide our decision-making.

Currently, digital and mobile technology is successfully being used to engage patients and to generate useful RWE on the management of AR. The freely available *Allergy Diary* (MASKair®) mobile app enables individuals to record daily data on the severity of allergic symptoms, work impairment, and medication use (the latter data are entered via a treatment scroll list that includes both prescribed and over-the-counter medications for AR localized for 22 countries: Argentina, Austria, Australia, Belgium, Brazil, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Lithuania, Mexico, Netherlands, Poland, Portugal, Spain, Sweden, Switzerland, and the UK) [38,39]. Because *Allergy Diary* (MASKair®) can distinguish between AR medications and record data on non-prescription medication use, it provides detailed and useful information on AR treatment, enabling the assessment of real-life treatment patterns. Real-life data collected from ~10,000 users of *Allergy Diary* (MASKair®) worldwide show that most patients are not being treated according to guidelines and often self-medicate [38–40].

Using RWE gathered by *Allergy Diary* (MASKair®) and other digital health apps and tools, the Mobile Airways Sentinel NetworK (MASK), a collaborative effort by the Allergic Rhinitis and its Impact on Asthma (ARIA) initiative, and professional and patient organizations in allergy and airway diseases, has proposed real-life integrated care pathways for individuals with AR [40]. To strengthen the conclusions drawn from real-world data, ARIA have proposed that Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria are applied to RWE. Moreover, they advise that next-generation guidelines for AR and asthma should include testing, refinement, and confirmation of guideline recommendations based on RWE in combination with the GRADE approach [40].

The methodology of RWE is a critical point for limiting the inherent risks of bias and interpreting the results. Matching procedures can minimize confounding bias, but not all of the other types of bias. RWE studies of AIT permit investigation of long-term clinical outcomes that may be too difficult or costly to evaluate in RCTs, such as the effectiveness of AIT for reducing AR symptoms at > 2 years post-treatment, and for delaying or preventing asthma progression and new asthma onset, in patients with grass or birch pollen-associated AR. The retrospective RWE studies that have been conducted to date show remarkably consistent results, and demonstrate benefits of grass and birch pollen AIT use that are sustained beyond treatment cessation; namely, significantly reduced AR symptomatic medication use, asthma medication intake, and initiation of asthma medication versus patients not using AIT, which reflects a significantly reduced progression of disease and significantly decreased risk of new-onset asthma. These effectiveness data obtained in the real-world setting mirror efficacy findings in RCTs, and should instill clinicians with confidence that AIT is a suitable choice for the management of symptoms in patients with grass and birch pollen-associated AR.

Funding

Medical writing support in the development of this manuscript was provided by James Reed, PhD of Newmed Publishing Services and funded by Stallergenes Greer in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

Declaration of Interest

P Devillier has received consultancy fees, honoraria for lectures, and/or research funding from ALK Abelló, Stallergenes Greer, AstraZeneca, Chiesi, Boehringer-Ingelheim, GlaxoSmithKline, Mylan, Novartis, Sanofi and Yslab. P Demoly has received consultancy fees from ALK Abelló, Stallergenes Greer, ASIT Biotech, Sanofi REGENERON, Bausch & Lomb, AstraZeneca and ThermoFisher Scientific; lecture fees from Mylan, Chiesi, ALK Abelló and Stallergenes Greer. M Molimard discloses board membership and consultancy with ALK Abelló, AstraZeneca, Boehringer-Ingelheim, GSK, Novartis Pharma, Sanofi, Stallergenes Greer and Zentiva; payment for travel/accommodation/meeting expenses from Novartis Pharma. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer Disclosures

A reviewer on this manuscript has disclosed that they are a scientific consultant for Stallergenes-Greer. Peer reviewers on this manuscript have no other relevant financial or other relationships to disclose.

ORCID

Philippe Devillier http://orcid.org/0000-0001-6054-1886
Pascal Demoly http://orcid.org/0000-0001-7827-7964
Mathieu Molimard http://orcid.org/0000-0002-4346-8346

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Halken S, Larenas-Linnemann D, Roberts G, et al. EAACI guidelines on allergen immunotherapy: prevention of allergy. Pediatr Allergy Immunol. 2017;28(8):728–745.
2. Bousquet J, Pfaar O, Togias A, et al. ARIA care pathways for allergen immunotherapy. Allergy. 2019;74(11):2087–2102.
3. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008. Allergy. 2008;63(Suppl 86):8–160.
4. Roche N, Anzueto A, Bosnic Anticevich S, et al. The importance of real-life research in respiratory medicine: manifesto of the Respiratory Effectiveness Group: Endorsed by the International Primary Care Respiratory Group and the World Allergy Organization. Eur Respir J. 2019;54(3):1901511.
5. Devillier P, Wahn U, Zielen S, et al. 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(12):1199–1206.
•• **Further results from a retrospective, real-world database analysis confirming the real-life benefits of 5- and 1-grass-pollen SLIT tablets in slowing AR progression, reducing the risk of new-onset asthma and slowing asthma progression in patients followed for up to 6 years after treatment cessation.**
6. Murphy K, Gawchik S, Bernstein D, et al. A phase 3 trial assessing the efficacy and safety of grass allergy immunotherapy tablet in subjects with grass pollen-induced allergic rhinitis with or without conjunctivitis, with or without asthma. J Negat Results Biomed. 2013;12:10.
7. Ozdoganoglu T, Songu M. The burden of allergic rhinitis and asthma. Ther Adv Respir Dis. 2012;6(1):11–23.
8. Bufe A, Ziegler-Kirbach E, Stoeckmann E, et al. Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. Allergy. 2004;59(5):498–504.
9. Röder E, Berger MY, Hop WC, et al. Sublingual immunotherapy with grass pollen is not effective in symptomatic youngsters in primary care. J Allergy Clin Immunol. 2007;119(4):892–898.
10. Cziraky M, Pollock M. Applied clinical trials. Real-world evidence studies 2015 [March 2019]. Available from: https://www.appliedclinicaltrialsonline.com/real-world-evidence-studies
11. Herland K, Akselsen JP, Skjonsberg OH, et al. How representative are clinical study patients with asthma or COPD for a larger "real life" population of patients with obstructive lung disease? Respir Med. 2005;99(1):11–19.
12. Costa DJ, Amouyal M, Lambert P, et al. How representative are clinical study patients with allergic rhinitis in primary care? J Allergy Clin Immunol. 2011;127(4):920–926e1.
13. Price D, Brusselle G, Roche N, et al. Real-world research and its importance in respiratory medicine. Breathe (Sheff). 2015;11(1):26–38.
14. Blonde L, Khunti K, Harris SB, et al. Interpretation and impact of real-world clinical data for the practicing clinician. Adv Ther. 2018;35(11):1763–1774.
15. Devillier P, Molimard M, Ansolabehere X, et al. Immunotherapy with grass pollen tablets reduces medication dispensing for allergic rhinitis and asthma: A retrospective database study in France. Allergy. 2019;74(7):1317–1326.
•• **This retrospective database study in France showed that grass pollen SLIT potentially reduces asthma progression in patients with AR in routine clinical practice, using medication dispensing as a proxy for disease diagnosis and progression.**
16. Schmitt J, Schwarz K, Stadler E, et al. Allergy immunotherapy for allergic rhinitis effectively prevents asthma: results from a large retrospective cohort study. J Allergy Clin Immunol. 2015;136(6):1511–1516.
•• **This seminal paper describing a large retrospective cohort study of a German national health insurance database demonstrated that AIT effectively prevents asthma in patients with AR in the real-world setting.**
17. Wahn U, Bachert C, Heinrich J, et al. Real-world benefits of allergen immunotherapy for birch pollen-associated allergic rhinitis and asthma. Allergy. 2019;74(3):594–604.
•• **In this retrospective cohort analysis of a German longitudinal prescription database, 6 types of birch pollen AIT significantly**

reduced AR and asthma medication intake, and significantly decreased the risk of new-onset asthma medication use, for up to 6 years after treatment cessation in routine clinical practice.

18. Zielen S, Devillier P, Heinrich J, et al. Sublingual immunotherapy provides long-term relief in allergic rhinitis and reduces the risk of asthma: A retrospective, real-world database analysis. Allergy. 2018;73(1):165–177.

•• **In this retrospective analysis of a German longitudinal prescription database, treatment with grass pollen SLIT was associated with slower AR progression, reduction in new-onset asthma, and slower asthma progression in the real-world setting, with a post-treatment effect of at least 2 years.**

19. Didier A, Wahn U, Horak F, et al. Five-grass-pollen sublingual immunotherapy tablet for the treatment of grass-pollen-induced allergic rhinoconjunctivitis: 5 years of experience. Expert Rev Clin Immunol. 2014;10(10):1309–1324.
20. Voltolini S, Modena P, Minale P, et al. Sublingual immunotherapy in tree pollen allergy. Double-blind, placebo-controlled study with a biologically standardised extract of three pollens (alder, birch and hazel) administered by a rush schedule. Allergol Immunopathol (Madr). 2001;29(4):103–110.
21. Worm M, Rak S, de Blay F, 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(1):7.
22. Canonica GW, Cox L, Pawankar R, et al. Sublingual immunotherapy: World Allergy rganization position paper 2013 update. World Allergy Organ J. 2014;7(1):6.
23. Casale TB, Canonica GW, Bousquet J, et al. Recommendations for appropriate sublingual immunotherapy clinical trials. J Allergy Clin Immunol. 2009;124(4):665–670.
24. Shamji MH, Kappen JH, Akdis M, et al. Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: an EAACI position paper. Allergy. 2017;72(8):1156–1173.
25. Calderón MA, Frankland AW, Demoly P. Allergen immunotherapy and allergic rhinitis: false beliefs. BMC Med. 2013;11:255.
26. Calderón MA, Cox L, Casale TB, et al. Multiple-allergen and single-allergen immunotherapy strategies in polysensitized patients: looking at the published evidence. J Allergy Clin Immunol. 2012;129(4):929–934.
27. Demoly P, Okamoto Y, Yang WH, et al. 300 IR HDM tablet: a sublingual immunotherapy tablet for the treatment of house dust mite-associated allergic rhinitis. Expert Rev Clin Immunol. 2016;12(11):1141–1151.
28. Jutel M, Agache I, Bonini S, et al. International consensus on allergy immunotherapy. J Allergy Clin Immunol. 2015;136(3):556–568.
29. Saturni S, Bellini F, Braido F, et al. Randomized controlled trials and real life studies. Approaches and methodologies: a clinical point of view. Pulm Pharmacol Ther. 2014;27(2):129–138.
30. Howarth P, Malling HJ, Molimard M, et al. Analysis of allergen immunotherapy studies shows increased clinical efficacy in highly symptomatic patients. Allergy. 2012;67(3):321–327.
31. Sade K, Berkun Y, Dolev Z, et al. Knowledge and expectations of patients receiving aeroallergen immunotherapy. Ann Allergy Asthma Immunol. 2003;91(5):444–448.
32. Allam JP, Andreasen JN, Mette J, et al. Comparison of allergy immunotherapy medication persistence with a sublingual immunotherapy tablet versus subcutaneous immunotherapy in Germany. J Allergy Clin Immunol. 2018;141(5):1898–901 e5.
33. Incorvaia C, Mauro M, Leo G, et al. Adherence to sublingual immunotherapy. Curr Allergy Asthma Rep. 2016;16(2):12.
34. Lemberg ML, Berk T, Shah-Hosseini K, et al. Sublingual versus subcutaneous immunotherapy: patient adherence at a large German allergy center. Patient Prefer Adherence. 2017;11:63–70.
35. Senna G, Caminati M, Canonica GW. Safety and tolerability of sublingual immunotherapy in clinical trials and real life. Curr Opin Allergy Clin Immunol. 2013;13(6):656–662.
36. Bachert C, Larche M, Bonini S, et al. Allergen immunotherapy on the way to product-based evaluation – a WAO statement. World Allergy Organ J. 2015;8(1):29.
37. Pfaar O, Lou H, Zhang Y, et al. Recent developments and highlights in allergen immunotherapy. Allergy. 2018;73(12):2274–2289.
38. Bedard A, Basagana X, Anto JM, et al. Mobile technology offers novel insights into the control and treatment of allergic rhinitis: the MASK study. J Allergy Clin Immunol. 2019;144(1):135–43 e6.
39. Bousquet J, Devillier P, Arnavielhe S, et al. Treatment of allergic rhinitis using mobile technology with real-world data: the MASK observational pilot study. Allergy. 2018;73(9):1763–1774.
40. Bousquet JJ, Schunemann HJ, Togias A, et al. Next-generation ARIA care pathways for rhinitis and asthma: a model for multimorbid chronic diseases. Clin Transl Allergy. 2019;9:44.

• **Demonstration of how RWE obtained through mobile technology has been used by ARIA to develop next-generation guidelines and integrated care pathways for patients with rhinitis and asthma.**