Real-world evidence for the long-term effect of allergen immunotherapy: current status on database-derived studies

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Abstract

Background: Randomized controlled trials (RCTs) are the gold-standard for benefit-risk assessments during drug approval processes. Real-word data (RWD) and the resulting real-world evidence (RWE) are becoming increasingly important for assessing the effectiveness of drug products after marketing authorization showing how RCT results are transferred into real life care. The effectiveness of allergen immunotherapy (AIT) has been assessed in several RWE studies based on large prescription databases. **Methods:** We performed a literature search for retrospective cohort assessments of prescription databases in Europe to provide an overview on the methodology, long-term effectiveness outcomes and adherence to AIT. **Results:** 13 respective publications were selected. AIT was more effective in reducing the progression of allergic rhinitis (AR) compared to a non-AIT control group receiving only symptomatic treatment for AR for up to 6 years. The development and progression of asthma was hampered for most endpoints in patients treated with most preparations compared to the non-AIT group, receiving only anti-asthmatic medication. The results for "time to onset" of asthma were inconsistent. Adherence to AIT decreased during the recommended 3-years treatment period, however in most studies higher adherence to subcutaneous than to sublingual AIT was shown. **Conclusion:** The analysis of long-term effectiveness outcomes of the RWE studies based on prescription databases confirms the long-term efficacy of AIT demonstrated in RCTs. Progression of rhinitis and asthma symptoms as well as delayed onset of asthma triggered by different allergens, real life adherence to the treatment shows differences in particular application routes.

Real-world evidence for the long-term effect of allergen immunotherapy: current status on database-derived studies

Short title: Narrative Review of Real-World Evidence in AIT

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Methods: We performed a literature search for retrospective cohort assessments of prescription databases in Europe to provide an overview on the methodology, long-term effectiveness outcomes and adherence to AIT.

Results: 13 respective publications were selected. AIT was more effective in reducing the progression of allergic rhinitis (AR) compared to a non-AIT control group receiving only symptomatic treatment for AR for up to 6 years. The development and progression of asthma was hampered for most endpoints in patients treated with most preparations compared to the non-AIT group, receiving only anti-asthmatic medication. The results for "time to onset" of asthma were inconsistent. Adherence to AIT decreased during the recommended 3-years treatment period, however in most studies higher adherence to subcutaneous than to sublingual AIT was shown.

Conclusion: The analysis of long-term effectiveness outcomes of the RWE studies based on prescription databases confirms the long-term efficacy of AIT demonstrated in RCTs. Progression of rhinitis and asthma symptoms as well as delayed onset of asthma triggered by different allergens, real life adherence to the treatment shows differences in particular application routes.

Keywords: allergic rhinitis, allergic asthma, allergen immunotherapy, long-term efficacy, real-world evidence

Introduction

AIT is the only treatment option that targets the underlying pathophysiology of allergy and therefore shows disease-modifying effects (1,2). A number of randomized controlled trials (RCTs) demonstrated long-term clinical efficacy persisting for years after treatment discontinuation (3,4). There is also evidence that AIT

can prevent the development of new sensitizations and reduce the risk of subsequent asthma development in patients with AR (5).

In 1964, the first randomized, double-blind, placebo-controlled study using subcutaneous immunotherapy (SCIT) for the treatment of IgE-mediated allergies to inhalant allergens was conducted (6). Starting from that point, many RCTs proved efficacy and safety for several seasonal and perennial allergens in allergic rhinitis/rhinoconjunctivitis and/or asthma (1,2,7,8).

RCTs are still considered as best and most reliable way to assess the efficacy and safety of an AIT product. The majority of statements in clinical guidelines are given on the basis of results received from RCTs. One key feature of RCTs is that they include an 'ideal' study population because they follow strict inclusion and exclusion criteria and study protocols. Thus they inevitably lack external validity since extrapolations to patients in real life are difficult. In contrast, real-world data (RWD) analyses include higher patient numbers using variable treatment patterns and a wide range of different alternative interventions applied by many physicians in daily practice (9). RWD can focus on the epidemiology, effectiveness, safety, medication adherence or cost of treatment related to a single drug or drug class but also provide long-term follow-up data beyond the time horizon observed in RCTs (9). These can be derived from different sources such as patient registries, health care databases, electronic health records, patient networks, and patient-generated data from wearables. Patient registries collecting data prospectively, in a cohesive way, with using standardized protocols are proposed to provide a higher quality of evidence than those collected retrospectively (10). All RWD can serve as a basis for real-world evidence (RWE) and provide additional insights into a patient's health status or use of drugs to supplement RCTs (11).

Concerning the assessment of both, RCT data and RWD in AIT, the aspect of different application routes - subcutaneous (SCIT) and sublingual (SLIT) tablets or drops – has to be considered. The underlying immune modulating mechanisms are slightly different (12,13). In addition, there are many different products on the market which differ in the allergen extract used, manufacturing process, doses, and dosing regimens. Taking this into consideration, the broad diversity of AIT products requires the proof of efficacy for each individual product in RCTs which also applies for RWE with regard to effectiveness.

This review focuses on analysis of retrospective multicentre database real-world evidence studies on AIT preparations with respect to long-term effectiveness and medication adherence. The chosen studies are ranked a middle quality in the hierarchy of AIT in real-world evidence proposed in an EAACI position paper in 2021 (10).

Methods

We performed a literature search in PubMed for full-text publications dealing with retrospective cohort assessments of prescription databases in Europe, which investigated AIT products from the real-world perspective. We used the search profile ((desensitization, immunologic OR sublingual immunotherapy OR subcutaneous immunotherapy) AND ((retrospective database) OR (real world evidence) OR (medication adherence AND retrospective)) and included all respective publications until March 31,2022.

Data for long-term effectiveness in allergic rhinitis, allergic asthma, time to onset of asthma and medication adherence were summarized and evaluated.

Results

Literature Search

The literature search in PubMed resulted in 13 publications (14–26). For key characteristics of the studies see Tables S1 (grass pollen studies), S2 (tree pollen studies), S3 (house dust mite (HDM) studies) and S4 (studies not differentiating between allergens) in supplementary information. Some analyses were funded by manufacturers of AIT preparations like the ReWARD (Real World Evidence in Allergy Research and Development) program by Allergopharma GmbH & Co. KG, Germany (14,15,17), the BREATH (Bringing Real-World Evidence to Allergy Treatment for Health) program by Stallergenes Greer, France (18,19,21,22) with Devillier et al. 2017 (22) representing a subanalysis of Zielen et al. (21) and the REACT (Real world effectiveness in allergy immunotherapy) study by ALK-Abelló, Denmark (25). ALK-Abelló, Denmark supported two further studies (16,26). Additionally, there are three publications focussing on medication adherence; one each initiated by ALK-Abelló (20) and Stallergenes Greer (23), while no company funding is mentioned in the third one (24).

The analyses were carried out using retrospective prescription databases from

- IMS LRx, IQVIA, Germany, formerly named LRx, IMS Health, covering about 60% of the statutory healthcare prescriptions in Germany (14,15,17,19,21,22),
- IQVIA France covering 34% of the nationwide retail pharmacies (18),
- AOK Plus Saxony, a regional sick fund, covering 55% of the population from the federal state of Saxony, Germany (16,26),
- Betriebskrankenkasse (BKK), Germany, a branch of the statutory health insurance including approx. 9 million patients (25),
- the German IMS Health Disease Analyzer database which is derived from electronic medical records from a panel of German general practitioners and other office-based, specialist physicians: The coverage comprised 13.4 million patients during the analysis period (20),
- PHARMO Record Linkage system, a network of linked databases providing drug-dispending records from community pharmacies from the Netherland which covered roughly one eighth of the total Dutch population (24),
- Patient Tracking National database provided by INSIGHT Health GmbH, Germany (23).

The data mostly include demographic information (sex and age) and information related to prescriptions, e.g. product, pack size, pack count and prescriber. Diagnoses according to the International Statistical Classification of Diseases and Related Health Problems-10 (ICD-10) codes were available in three studies (16,25,26).

Each of the studies listed has defined exclusive inclusion and exclusion criteria, which may be found in the respective original publications.

The 13 publications presented data on effectiveness and/or medication adherence for AIT in general, preparation groups or single SCIT and SLIT products. Some of the assessments focused on certain allergens (grass pollen, tree pollen, house dust mites), while others did not.

Most of the assessments investigating effectiveness of AIT consistently predefined different time intervals before (pre-index period), during (treatment period) and after AIT application (follow-up period) (15,17–19,21,22). In other assessments, the whole period after receiving the first AIT prescription was designated as follow-up period (16,25,26).

Effectiveness of AIT was calculated by comparison to a Non-AIT control group receiving prescriptions of symptomatic medication for the treatment of AR and/or anti-asthmatic medication for the treatment of asthma.

Non-AIT control patients were matched with patients receiving AIT in order to minimize confounding bias. An 'exact matching' method was conducted in 6 studies (15,17–19,21,22) on the basis of several variables, e.g. age class, sex and asthma status. In one analysis 'propensity score matching' was performed (25).

In this overview, we focus on data concerning the long-term effectiveness of AIT, i.e. during the full analysis period (treatment plus follow-up period) and follow-up periods as well as medication adherence.

1) Long-term effectiveness of AIT was evaluated by means of the following endpoints:

- progression of allergic rhinitis: based on a comparison of the number of prescriptions for symptomatic treatment of AR (e.g. nasal corticosteroids, antihistamines) with or without allergic conjunctivitis during follow-up vs. pre-index compared to a Non-AIT group receiving only anti-symptomatic treatment.
- progression of asthma in patients with asthma at pre-index period: based on a comparison of the number of prescriptions for asthma medication (e.g. long-acting beta-agonists (LABAs), inhaled corticosteroids (ICSs), combinations of LABAs and inhaled corticosteroids (ICSs), methylxanthines, leukotriene antagonists, short-acting beta-agonists (SABAs)) in AIT-treated vs. Non-AIT control patients.
- incidence of asthma in patients without asthma at pre-index period: development of asthma based on prescriptions for anti-asthmatic medication compared to the Non-AIT control group.
- time to onset of asthma after starting AIT.

2) **Medication adherence to AIT** was evaluated based on different definitions: adherence, compliance, persistence and/or days on therapy.

Long-Term Effectiveness

Progression of allergic rhinitis

Six of the RWE studies evaluating progression of grass pollen-, tree pollen- or house dust mite-allergic rhinitis showed that all investigated SCIT and SLIT preparations or preparation groups were significantly more effective compared to symptomatic treatment for up to 6 years follow-up (15,17–19,21,22). In another analysis, rhinitis prescriptions were significantly reduced during the years 1 and 4 to 7, when assessed cross-sectionally year by year (25).

Two assessments confirmed the effectiveness in children suffering from grass pollen-, tree pollen- and HDM-AR when being treated with different SCIT and SLIT preparations (15,17). Another study even showed a significantly higher effect for two grass pollen SLIT tablets in patients below the age of 18 compared to adults (21). Stronger reductions in AR prescriptions were shown across various AIT subgroups compared to Non-AIT (e.g. grass and tree pollen AIT, HDM AIT, children, adults, native allergens, allergoids, SCIT, SLIT drops and SLIT tablets for the 3rd year of the assessed period of 9 years (25). Whether these differences reached significance was not shown. For details, see tables S5, S6, S7, S8 in supplementary information.

Progression of asthma

Eight of the RWD analyses examined the effectiveness of AIT on asthma progression for up to six years follow-up resp. the full analysis period of 9 years (15–19,21,22,25) showing more heterogenous results than those for progression of allergic rhinitis. In 4 studies all investigated AIT-groups required significantly fewer asthma prescriptions than the corresponding Non-AIT group (15,18,19,21) while other analyses failed to show significant effects for all AIT preparations, age groups, timepoints and/or endpoints (16,17,22,25). Investigating the effect over time by cross-sectional comparisons to the control group, one assessment found that during the years 4 – 6 significantly less AIT-treated patients required asthma medication whereas asthma prescriptions were significantly reduced for up to 7 years after starting AIT. In addition, in the AIT group there was a significantly increased likelihood of stepping asthma treatment down as well as a significantly lower risk of stepping up (25). For details see tables S5, S6, S7, S8 in supplementary information.

Development of asthma

Seven studies aimed to investigate whether AIT is able to prevent the occurrence of asthma in patients

suffering from AR during the full analysis and/or follow-up period (15,17–19,21,22,25,26). Most assessments indicated that the risk of incident asthma was significantly lower in patients with AR exposed to AIT compared with that in the Non-AIT group regardless of the type of AIT (SCIT or SLIT), the preparation studied (allergoid or natural allergen preparation), or the type of allergen (HDM, birch or grass pollen, all allergens) for up to 9 years follow-up. Nevertheless, the results were not constantly significant at certain analytical time periods (19,22), for single preparations or preparation groups (22,26) or for the age group of children (15). The only study comparing the risk in adults and children/adolescents did not show a significant difference for follow-up and full analysis periods (21). For details see tables S5, S6, S7, S8 in supplementary information.

Time to onset of asthma

When evaluating time to onset of asthma in patients with no asthma at inclusion, conflicting results were shown. For grass pollen SLIT tablets the time to onset of asthma was significantly longer compared to the control group during the 6-years follow-up period (21) while the risk was significantly increased (hazard ratio (HR): 1.22 (1.12 – 1.32); $p < 0.001$) for the AIT group in another study (25). The authors assumed that a higher frequency of specialist visits in the AIT group led to more ICD10 coding for asthma. For details see tables S5 and S8 in supplementary information.

Medication adherence

Seven RWE studies examined adherence to medication (14,15,17,20,23–25). Most assessments used different terms and adherence definitions, e.g. adherence, persistence, compliance, making direct comparisons difficult. Nevertheless, studies evaluating the recommended three-years' time horizon for AIT showed that medication adherence decreased over the therapy years (14,15,17,20,23,24). Three studies showed that adherence and compliance were significantly higher with SCIT than with SLIT treatment (14,17,24). Results for days on therapy confirmed this result (14,17). One study contrasted these results with a higher persistence with SLIT than with SCIT (23) while another one showed comparable adherence to and persistence with SLIT and SCIT (20). For details see tables S5, S6, S7, S8 in supplementary information.

Discussion

Importance of RWD Analyses

DBPC trials are considered the gold-standard for evaluating efficacy since they prevent systematic bias in allocation of treatment and are demanded by regulatory authorities for gaining marketing authorizations. Nevertheless, there are some limitations because of restricted study durations, small numbers of patients, controlled settings and the placebo effect (10,11,27,28). The missing external validity leads to a low generalizability because RCTs are performed in conditions very different from daily practice (28): patients in daily practice are more often diverse especially concerning age, sex or concomitant diseases which may have an impact on treatment efficacy (27,29). In contrast, RWD have high generalizability since they investigate effectiveness under routine circumstances (28) and they offer the option for long-term evaluations. The data can be analysed within a short time, in patient groups that are usually not included in RCTs (e. g. patients with comorbidities), in different age groups and with a manageable investment.

Some signals or effects may even show up only in RWD studies. In a structured literature review, Elliot et al. compared hypoglycemia event rates/patient/year in type 1 diabetes mellitus (T1DM) and insulin-treated type 2 diabetes mellitus (T2DM). In both patient groups, higher rates of hypoglycemia were observed in real-world settings compared to clinical trial settings, especially in patients with T1DM. The authors concluded that RCTs are likely to underestimate the burden of hypoglycemia in clinical practice (30). One of the studies included here showed that AIT treatment was associated with a significantly reduced likelihood of developing pneumonia and receiving antibiotics prescriptions compared to the Non-AIT control group (25). Due to the small proportion of patients suffering from pneumonia (1.4% in the AIT group, 2.0% in the Non-AIT control group) such significant differences would probably not show up in any RCT.

It may not be expected that the outcomes of RWD and RCT analyses are invariably congruent. One reason

for this is the so-called ‚efficacy-effectiveness gap', which means that the effectiveness in clinical practice is generally reduced compared to the efficacy shown in RCTs by transfer and implementation loss, e.g. delivery of care, adherence to treatment, and time between treatment and assessment of the outcome (31,32). Nevertheless, consistency between RWD and RCT data were already shown for indications like metastatic renal cell carcinoma when treated with the tyrosine kinase inhibitor sunitinib or the use of antipsychotics in schizophrenia (33,34).

RWD represent non-selected large patient groups therefore complementing but not replacing results from RCTs (10). There is increasing interest of regulatory authorities to evaluate the options that RWE may offer, e.g. with regard to 'identify areas of highest unmet needs where real world evidence (RWE) can supplement clinical trial data in regulatory decision making' (EMA/705364/2021; (35) (36). Since the methodological prerequisites are not fixed yet it probably will take some more years until RWD may be supportive in granting marketing authorizations for AIT products. Until now, the terms 'RWD' or 'RWE' are not used in the same way by different authorities (see Table S7 in supplementary information).

RWD Analyses on AIT Long-Term Effects

In contrast to symptomatic medication, AIT is the only causal treatment option for IgE-mediated allergic diseases and therefore has the potential for long-term effects that last after termination of therapy (1,2). There are a few RCTs showing long-term efficacy for single SCIT and SLIT preparations in allergic rhinitis (37–42) for up to five years after terminating three years of AIT. In children, one of these trials additionally showed a reduced risk of experiencing asthma symptoms or using asthma medication while there was no difference in time to onset of asthma during the two-year follow-up period (41). Data from different real-world settings e.g. non-interventional studies or analyses in claims databases, patients surveys, electronic health records or product and disease registries allow to analyze the effectiveness and medication adherence under practical conditions (10,43) and the evaluation of long-term data for larger patient populations and even longer follow-up periods without the risk of ethical concerns arising from withholding a therapy proven to be effective in placebo groups in 5-years' DBPC AIT studies.

This review summarizes results from thirteen publications dealing with retrospective cohort assessments of national prescription databases in Europe. All nine assessments investigating effectiveness consistently showed long-term effectiveness for AIT in allergic rhinitis for different time periods; long-term effectiveness for AIT in asthma as well as the asthma preventive effect was proven in most studies (15–19,21,22,25,26). Therefore, the findings from the RWD summarized here are in line with those observed in RCTs showing long-term effectiveness of AIT in allergic rhinitis and asthma as well as asthma preventive effects (37–42). Since national and international allergology societies (1,2,44) demand an individual product-based efficacy evaluation respective long-term RWD for more individual AIT preparations are desirable.

Limitations and Restrictions of AIT RWD Analyses

The results in real-world analyses summarized here have some limitations and restrictions, e.g. the validity of disease diagnoses (in most studies medication serves as a proxy to identify the disease) or the influence of OTC medication which is not included in prescription databases. Patients' drug consumption behavior is not analyzed, the severity of the disease and patients' symptom control is not known. The selection of control patients in the chosen matching process has a strong impact on the results. A detailed overview is given in Table S10 in the supplementary information.

Statistical Peculiarities in RWD Analyses on AIT

Non-randomized studies are subject to confounding since demographic and clinical patient characteristics influencing physicians' prescribing choices or affecting treatment outcomes may systematically differ between patient cohorts, resulting in a biased estimation of treatment effects (45). Established confounders are patient sex and age, differences in AR symptoms and disease severity before index, duration of AIT, and length of analysis periods. Other factors potentially causing the confounding variables not being properly balanced

are the lack of blinding and randomization, residual monitoring bias and confounding by indication (28). Matching methods attempt to approximate the ideal of randomized controlled trials despite using observational data. Two common matching methods are 'exact matching' (EM) and 'propensity score matching' (PSM) (45). EM uses the complete dataset to identify an exact match covering all confounding variables resulting in smaller variance of the treatment effect but greater danger of excluding cases. With increasing numbers of matching variables, the variability of the patient population is decreased but also the resulting study sample size is diminished. Hence, EM is applied when datasets covering a high patient count are available. On the other hand, with PSM, patients are matched on a single propensity score in order to identify not the exact but the nearest neighbor, i.e. the probability of receiving the exposure of interest given the observed baseline characteristics (45). This leads to an improved applicability in datasets with a high number of confounding variables available but bares the danger of greater variance (46). Both methods were used in the real-world analyses summarized on hand, EM in 6 studies (15,17–19,21,22), PSM in one study (25).

Effectiveness of AIT in RWD Analyses reflects Efficacy in RCTs

Tables S5, S6, S7, S8 in supplementary information summarize detailed results from the RWD analyses included. Taking a closer look at e.g. the effects on progression of allergic rhinitis using grass pollen AIT (Tab. S5), it is striking that the reduction in the use of antiallergic medication in the different assessments ranges from 18.8% to 75% compared to the non-AIT group. But comparing the results would be misleading since the assessments differed substantially concerning e.g. in-/exclusion criteria, matching process, evaluated antiallergic medication or calculation/statistical methods, even when performed in the same prescription database and nearly the same analysis periods. Therefore, the results from different assessments do not indicate that effectiveness is higher for any allergen (e.g. pollen vs. house dust mites) or allergen preparation (e.g. SLIT vs. SCIT; allergoids vs. unmodified preparations), especially since no direct comparisons between single AIT preparations or preparation groups were made within the same assessments.

In AIT RCTs, the primary endpoint is usually evaluated after one or two years of treatment whereas one key advantage of RWD is the possibility to evaluate data from longer observation periods. Despite this fact, we tried to check consistency between RCT efficacy and RWD effectiveness by using the medication scores from RCTs and the number of prescriptions in RWD analyses for preparations, which could be unambiguously identified in the RCT and RWD publications. For some preparations symptom medication (SMS) score data (47) or data on reduction of dose steps of inhaled corticosteroids (48) served as efficacy results in the RCTs in the absence of medication score data (see Table S 11 in supplementary information). The analysis proved that the efficacy shown in gold standard DBPC RCTs is rigorously confirmed in RWD over longer time periods.

Adherence to AIT Treatment in RWD Analyses

Like with any other chronic disease medication adherence to AIT is of high importance for treatment efficacy (1,2), but is generally lower than assumed by physicians (1).

Data on adherence were collected in 7 publications (14,15,17,20,23–25), where different terms (adherence, compliance, persistence) and definitions were used so that the results are difficult to compare. Definitions varied from defining patients being adherent or persistent when receiving just one prescription per year (20,23) to detailed calculation based on the potential expiry of single packages while defining maximum treatment or pharmacy visits gaps (14,17,24). In two assessments 'days on therapy' were defined as an additional parameter (14,17). In summary, the data consistently show that medication adherence drops during the three years of AIT independently from the preparation used.

Adherence data from RCTs cannot be transferred into real life since the conditions are completely different. Adherence is reported to be higher in clinical studies than in real-life surveys (2). RCTs follow a strict protocol, patients are often supervised by study nurses and might be paid for their participation so that adherence is artificially increased (14).

Three assessments resulted in a higher medication adherence to SCIT than to SLIT (14,17,24). The two assessments showing divergent results for persistence in the SLIT and SCIT sub-cohorts defined patients being persistent when receiving at least one prescription in both, the second and third year of AIT - thereby ignoring the application recommendations in the summary of product characteristics and so the range of coverage of the single packs available for each preparation (20,23). Nevertheless, the study by Allam et al. also showed that patients discontinued SLIT in the first year of AIT more frequently than SCIT patients (20), which was also shown in other studies (14,17,24). The authors assume that early oral side effects during SLIT are particularly responsible for the higher discontinuation rates in the first year (20,24). Additionally, inconvenience, lack of efficacy or forgetfulness may drop adherence (2). Therefore, patient education and good communication between physicians and patients are fundamental for a good medication adherence (2). Improving AIT adherence is one of the most important future goals for ensuring efficacy (1) with some options being reminder mechanisms via mobile phones (e.g. alarms, short message service (SMS), apps) (2). Meanwhile some mobile phone apps are available but a meta-analysis found that most did not contain the desirable features and were of low quality (49). With the MASK-rhinitis (Mobile Airways Sentinel NetworK for allergic rhinitis) a patient-centred information and communication system is operational for patients suffering from allergic rhinitis in more than 20 countries (50). The mobile phone app MASK-air(r) was already used to investigate adherence to symptomatic treatment in patients suffering from allergic rhinitis indicating a low adherence in this real-world setting from a European population sample (49). Respective data for adherence to AIT are not yet available but desirable.

RWD in Cost-Effectiveness Studies

Management of patients suffering from AR results in high financial burden to patients, health-care providers and society (51). Several pharmacoeconomic studies conducted from a health system perspective in Europe and using QALYS as their outcome measure have reported strong evidence that AIT is cost-effective in the management of AR and asthma compared with symptomatic treatment alone (52–59). The magnitude of cost-effectiveness is likely underestimated because most of the studies did not consider long-term benefits or preventive and prophylactic effects but only costs during the treatment period (60). Cost-effectiveness studies for AIT are based on efficacy data from RCTs or metanalyses and usually include results for medication adherence from RWD. There are several analyses investigating cost-effectiveness of grass pollen AIT for different European countries using adherence data from various sources (52,54–56,58,59). All proved cost-effectiveness of SCIT and SLIT compared to symptomatic treatment for patients with allergic rhinitis or rhinoconjunctivitis. For AR, the most recent study analyzing the cost-effectiveness of a SCIT allergoid and a SLIT tablet in Germany showed that SCIT and SLIT are cost-effective compared to symptomatic treatment with SCIT appearing dominant due to higher patient adherence and lower drug costs (17,58). This cost-effectiveness study was the first using drug and treatment costs and RWD adherence data for the same preparations in the same country instead of including data of a combination of AIT preparations or data from other countries as a basis (52,54–56,59).

Conclusion

Real-world data for AIT complement those from randomized controlled trials. The RWE studies summarized in this review demonstrated the effectiveness of AIT in hampering the progression of rhinitis and asthma and onset of asthma for AIT with different allergens, AIT products, and for different age groups in daily practice. Data for medication adherence are more true-to-life when based on real-world data but due to divergent adherence definitions there are no consistent results in the different real-world assessments. Regulatory authorities are currently developing standards for generating and assessing RWE data to support regulatory decision-making for drug and biological products.

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Christian Vogelberg reports consulting fees and/or payment or honoraria for lectures, presentations or speakers bureaus from Allergy Therapeutics, Bencard Allergie, Allergopharma, HAL Allergy, Stallergenes Greer, Novartis Pharma, LETI Pharma, DBV Technology, Aimmune, Sanofi Aventis, ALK-Abello, Memberships: AeDA, GPA, APPA, DGAKI, EAACI.

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Author Contributions

All authors substantially conceived and designed concept, structure and design of the review, provided important intellectual input, contributed considerably to the analyses and interpretation of the data and have been involved in re-drafting the manuscript. CV, BB and MJ counter-checked the literature search, BB evaluated the methodology in the reviewed papers. All authors critically revised the manuscript and gave final approval of the version to be published. No honorarium, grant, or other form of payment was given to any of the authors to produce this manuscript.

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