Real-world evidence: Methods for assessing long-term health and effectiveness of allergy immunotherapy

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Recently, scientific societies and regulatory authorities have stressed the need for more robust real-world evidence (RWE) in allergic respiratory disease.[1-4] Despite the importance of complementing randomized clinical trials (RCTs) with high-quality RWE, and although a relative increase in the numbers of RWE studies (RWSs) in allergy immunotherapy (AIT) has been seen in recent years, the number of RWSs conducted in AIT is still limited[4] (Fig 1).

The highest level of evidence is suggested if coexisting RCTs and observational studies provide consistent findings.[2,5] If appropriate methods and standardized protocols are applied in RWSs there is the opportunity to transform real-world data into evidence of high clinical relevance consistent with the 2021 position of the European Academy of Allergy and Clinical Immunology.[2] However, even if RWSs are of good quality and scientifically reliable, the objective will be to assess associations, and in the case of AIT, studies are commonly conducted after a medicine has been marketed. RCTs are still needed to assess causal effects, which currently are the basis for obtaining regulatory approval and marketing authorizations for AIT. As the robustness of RWSs can be hampered by several factors, this article aims to identify the caveats and emphasize how the quality of RWSs can be improved by mirroring certain methodologic steps from RCTs.

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DATA SOURCES AND STUDY DESIGNS IN RWE

Selecting the appropriate data source is central for the quality of generated data. As heterogeneity of the study population is an intrinsic characteristic of RWSs, large cohorts are required. RWE may be generated prospectively through primary data collection or retrospectively by using secondary data sources (eg, registries, health care claims, or prescription databases), which have become more complete and comprehensive in recent years. Faced with the challenge of obtaining large enough sample sizes in AIT and the importance of looking at outcomes over long time horizons as AIT is a disease-modifying treatment, retrospective data sources are highly suitable. Although routinely collected health care data offer advantages in providing access to large representative samples of patients in routine clinical practice along with the potential for long-term follow-up, the data quality of such sources can be a challenge (ie, owing to erroneous data entries and incomplete data). Recent publications have discussed strengths and limitations of such data sources in AIT.[2,6] Because of differences in data collection, data protection issues, and restrictions in access to data sources, combining retrospective data sources globally remains a challenge. In AIT specifically, an additional challenge is the difference in treatment modalities and products available across the world. The following sections will focus on retrospective data sources and the assessment of effectiveness in RWSs.

GENERATION OF HIGH-QUALITY RWE

Conducting a high-quality and scientifically reliable RWS requires rigorous methodology largely mirroring what is done in RCTs, although without randomization, which alone provides unbiased estimates (Table I). Quality standards for reporting RCTs are well described in the Consolidated Standards of Reporting Trials (CONSORT) statement.[7] Frameworks to assess the quality of RWSs are described by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist[8] or the Real Life Evidence Assessment Tool (RELEVANT) tool, with key principles reflecting the requirements for RCTs.[4]

Prespecification and transparency

Hypotheses and research questions must be prespecified to avoid *post hoc* "fishing" for interesting outcomes.[4] Transparency

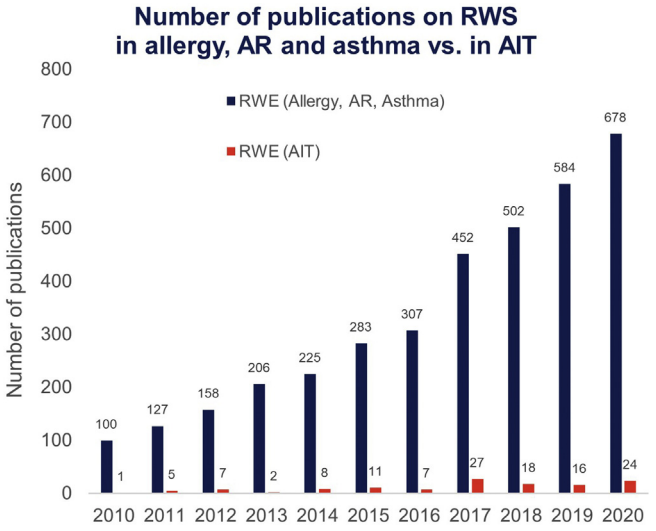

FIG 1. The number of published real-world evidence studies has increased significantly in the past 10 years within allergy, allergic rhinitis, and asthma, except for allergy immunotherapy, where real-world studies remain scarce. Search terms: (Real-world data OR Real-world evidence OR Registry) AND (asthma OR allergy OR allergic rhinitis) AND (allergy immunotherapy OR allergen immunotherapy), with or without AIT included. Results have been summarized by calendar year.

about the study design and analysis before execution is key and requires preregistration of the RWS in a public registry or publication of the study design and a prespecified statistical analysis plan.[4] Similar to an RCT, the prespecified analysis plan should include considerations about estimands and handling of intercurrent events and should also address the sample size and statistical power needed to detect differences. As in an RCT in which the population is selected according to eligibility criteria and the database is locked before unblinding of the results, an RWS should have prespecified enrollment criteria, and study cohorts can be locked before testing of the protocol-defined hypotheses.

Ensuring comparable groups to avoid confounding

To minimize the risk of bias and confounding, it is important to identify, control for, and address potential confounders in retrospective database studies.[4] Because of the absence of randomization, retrospective studies are subject to confounding by indication and/or disease severity in those cases in which exposure is associated with additional unmeasured risk (eg, in AIT studies, patients with allergic rhinitis [AR] who are treated with AIT are likely to have more severe AR than are those patients with AR who are not treated with AIT). Rosenbaum and Rubin, who derived the methods for propensity score analyses, pointed out that to be valid, exposure to the treatment of interest should be "strongly ignorable" as a source of additional information on underlying risk.[9] Hence, if a treatment is routinely given to higher-risk subjects, that risk must be described separately and accounted for.[9] The more dissimilar the compared groups, the greater the risk for confounding, and ideally, matching designs such as propensity score matching or instrumental variable techniques are used.[4] Comparison of the study groups at baseline before and after matching is important.[4] If key confounding variables differ at baseline, there is a higher likelihood for substantial confounding in the results.[4] To assess validity and potential confounding, RWSs should aim to replicate the findings of RCTs in similar populations where possible, before bridging into different populations and longer follow-up.

Predefined outcomes measured in a valid way and reported transparently

The primary outcome(s) must be defined and measured in a valid way. In retrospective studies, it is often necessary to use proxies for outcomes of effectiveness or disease severity (eg, in the case of AIT studies, the prescription medications for AR and asthma, as well as confirmed diagnoses, are used as proxies of disease severity in the lack of symptom scores).[4] RWS results should be presented for primary and secondary outcomes.[4] Study quality is enhanced if the outcomes are reported as absolute and relative measures.[4] The uncertainty of the findings (CIs) should be reported, as should the results of sensitivity analyses.[4]

Results in perspective of existing research

Findings should be adequately discussed in line with available information and their clinical relevance.[4] Limitations, including potential biases and confounding factors, should be described following a discussion on how these may influence the results.[4]

Transparency on conflict of interest

Any conflict of interest must be transparently reported,[4] and measures should be taken to mitigate the conflict of interest (eg, through involvement of third parties in the design, conduct, and analysis).[4]

Example: The Real-world Effectiveness in Allergy Immunotherapy (REACT) study

The aim of the REACT study was to assess the effectiveness of AIT and provide high-quality RWE regarding how AIT works in the long term and in real life.[10] In this retrospective database study, rigorous methodology was applied, comprising a prespecified objective and processes that were described in the protocol, preregistration at ClinicalTrials.gov, and cohort lock before outcomes analyses; in addition, all analyses were conducted by an independent third party. Propensity score matching was used to ensure comparable groups and mitigate confounding. Subjects were matched 1:1 by using the nearest neighbour approach without replacement with a caliper of 0.01, based on 30 variables available in the database, including demographics, diagnosis codes for relevant comorbidities, prescriptions for AR and asthma medication, health resource utilization, and costs. The standardized mean differences for variables included in the matching had to be less than 10%. The study found that AIT was associated with greater reductions in AR and asthma prescriptions (both controller and reliever medication) compared to control subjects.[10] The AIT group had a significantly greater likelihood of stepping down asthma treatment ($P < .0001$).[10] On top of the reduction in asthma treatment, a greater reduction in severe asthma exacerbations was seen in the AIT group ($P < .05$).[10] Reductions in pneumonia managed with antibiotic prescriptions, hospitalizations, and duration of inpatients stays all favored AIT.[10] The findings of the REACT study complement the existing

TABLE I. Key methodologic aspects for assessing the effects of AIT in retrospective RWSs of high quality by mirroring RCTs

Methodologic aspect	RCTs	Retrospective real-world evidence studies
Transparency	Preregister the study protocol in a public registry or report the study design in a publication	Preregister the study protocol in a public registry or report the study design in a publication
	Report conflicts of interest and follow ICMJE authorship recommendations	Report conflicts of interest and follow ICMJE authorship recommendations
	Adhere to reporting standards (eg, CONSORT)	Adhere to reporting standards (eg, STROBE)
Minimize risk of bias and confounding	Prespecify eligibility criteria, outcomes, and statistical analyses plan	Prespecify eligibility criteria, outcomes, and statistical analyses plan
	Ensure comparable groups through randomization	Ensure comparable groups through appropriate methods (eg, propensity score matching)
Analyses	Efficacy of AIT is assessed by using daily diaries and often reported as the total combined score, daily symptoms score, daily medication score, and Rhinitis Quality of Life Questionnaire score	Effectiveness of AIT can be assessed by using proxies such as prescriptions, diagnosis codes, health care resource utilization, and cost
	Database lock before analyses and/or unblinding	Cohort lock before analyses
Interpretation	Identify key strengths and limitations and critically discuss results	Identify key strengths and limitations, and critically discuss results in the context of existing RCT evidence

CONSORT, Consolidated Standards of Reporting Trials; *ICMJE*, International Committee of Medical Journal Editors; *STROBE*, Strengthening the Reporting of Observational Studies in Epidemiology.

evidence from RCTs in AIT and support the clinical decision making regarding use of AIT for the treatment and sustained control of AR and asthma.[10]

With an increasing amount of data, researchers have unique opportunities to generate valid and good-quality RWE of the effectiveness of AIT with the application of rigorous and high scientific standards. Although the focus herein was retrospective RWS, other RWE study types will likely benefit from using clinical RCT knowledge. Altogether, robust assessments of the effectiveness of AIT in RWSs complement the existing evidence of effect and safety of AIT in RCTs.

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