



Evidence-Based Medicine and Real-World Data in Allergen Immunotherapy Today and in the Future: Quality or Quantity?

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Abstract

Purpose of the review Data obtained from controlled clinical trials remains the gold standard for the evaluation of treatment efficacy and safety. This information is used in systematic reviews and meta-analysis providing data for evidence-based medicine (EBM) statements and conclusions which are preferred by regulatory and academic groups when decisions and recommendations need to be given.

Recent findings: The quantity and diversity of real-world data (RWD) have been increasing exponentially as technology and integrated electronic medical records have made this information increasingly accessible and useful for outcomes research and regulatory purposes.

There are increasing interest and potential for converting RWD into real-world evidence that, through careful analysis and interpretation, can be used to inform healthcare decision-making.

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Summary In this article, we present a concise summary of the literature about the role of EBM and RWD in allergen immunotherapy. We are aiming to evaluate their influence on current and future decisions for good clinical practice parameter recommendations.

Introduction

Over the years, concepts in science and medicine could be maintained, but the evidence accumulated regarding the efficacy and safety of any particular therapeutic intervention would unavoidably change. This affects its original decisive weight and may change its original influence when decisions need to be taken for the individual and collective care of patients and for the making of clinical guidelines.

This article presents a concise compilation of the literature about the role of evidence-based medicine (EBM) and real-world data (RWD) in allergen immunotherapy (AIT). We are aiming to evaluate their influence on current and future decisions for good clinical practice parameters recommendations.

Clinical practitioners and regulatory and health-related decision makers should estimate the value of each AIT study and product in a comprehensive manner. They should consider the importance of complementing (i) the clinical evidence, generated on specific product clinical development programme or systematic reviews, with (ii) clinical observation evidence obtained after AIT product is registered for commercialization.

We will follow a chronological order starting from the concept or idea of drug development, to pharmaceutical development, to collecting efficacy and safety data, to the preparation of clinical recommendations and/or guidelines of that specific AIT product for real clinical practice, based on EBM and RWD.

Clinical development of a therapeutic intervention

Pharmaceutical agent development

This is the process of bringing a new pharmaceutical agent to the market once a principal compound has been identified through the process of drug discovery. It includes pre-clinical research on microorganisms and animals, filing for regulatory status for an “investigational new pharmaceutical agent” to initiate clinical trials on humans. This includes the step of obtaining regulatory approval with a new pharmaceutical agent application to market the drug.

Clinical development

A proper clinical development programme should cover the clinical trial phases I, II and III. The aim is to collect data that will be used to prepare a “dossier of registration” that the competent regulatory authorities, through their experts, will evaluate. Then, they will decide to approve or reject commercialization. If authorized, the new product can be prescribed and used by the patients (see Table 1).

EBM

EBM definition

EBM is “*the conscientious explicit and judicious use of current best evidence in making decisions about the care of individual patients*” [1]. The concept is to assure that

Table 1. Clinical phases of a good clinical development programme

Phase 0	Trials for pharmacokinetics, oral bioavailability and half-life of the drug
Phase I	Trials of testing of the drug on healthy volunteers or few patients for safety; involves testing multiple doses (dose-ranging)
Phase II	Trials of testing of the drug on patients with a specific disease to assess efficacy and side effects. Most of the times, these are placebo-controlled trials. Sometimes, phase II of a clinical trial is divided into: • Phase IIa: to evaluate short-term safety of a drug • Phase IIb: to confirm the clinical efficacy of a drug and determine the therapeutic dose range or analyse some pharmacodynamic parameters (onset of action, pharmacokinetics, etc.)
Phase III	Trials are large, pivotal trials to determine safety and efficacy in sufficiently large numbers (hundreds) of patients with a targeted well-defined disease. If safety and efficacy are adequately proved, clinical testing may stop at this step. They can last from several months to several years and should be randomized trials. Phase III trials test the ultimate safety, efficacy and dosage of drugs as compared with the current gold standard treatment or placebo. Dosage levels will be modified to determine the dosage that provides the most beneficial effects while offering the least negative side effects. During phase III research, the efficacy of the drug on various levels of the disease is also tested. Though making it phase III trials is unlikely for drugs, almost 80% of those that do enter phase III trials move on to phase IV trials.
Phase IV	Trials are post-approval that are sometimes a condition attached by the corresponding health regulatory agency, also called post-marketing surveillance studies.

when decisions are taken they are made on the basis of the most up-to-date, solid, reliable, scientific evidence. In the case of medicine or health care, these are the decisions about the care of individual patients.

Categorizing the evidence

Summarised evidence is categorised to reflect its susceptibility to bias. “*Strength of evidence classification schemes*” has been accepted and used in several systematic reviews (SRs) [2].

Most of the current assessments of evidence for AIT follow the Shekelle’s scheme of “levels of evidence and strength of recommendation”.

These concepts constitute the supporting statements for the development of clinical practice guidelines [2, 3••, 4–6].

Systematic reviews

SRs are conducted to “*identify, classify, categorize and assess the current existing evidence on the efficacy and safety on any therapeutic intervention*”.

The purpose of any SR is to collect all available evidence, assess its potential applicability to a clinical question or hypothesis under consideration, examine the evidence for susceptibility to bias and extract and condense the findings in a clear and practical manner.

Questions of the efficacy of interventions usually mean that randomised controlled trials (RCTs) should be required, while questions of risk usually mean that prospective cohort studies should be sought.

Data from SRs are usually presented in a form that allows comparison of the designs and results of the extracted studies.

Meta-analysis

A meta-analysis (MA) is “the statistical procedure for combining data from multiple studies”. When the treatment effect (or effect size) is consistent from one study to the next, MA can be used to identify this common effect. Where appropriate, MA can be used to summarise the results of multiple studies.

MA is often, but not always, an important component of a SR procedure. For instance, a MA may be conducted on several clinical trials of a medical treatment, in an effort to obtain a better understanding of how well the treatment works [3••, 4, 7, 8••].

However, we must consider the limitations of SRs and MA as a consequence of the clinical and methodological heterogeneity found in most of these evaluations [8••, 9].

1. *Clinical heterogeneity* includes variability in the participants (children vs adults), variability in interventions (subcutaneous (SCIT) vs sublingual (SLIT) AIT) and variability in clinical outcomes.
2. *Methodological heterogeneity* includes variability in the trial design, study quality, allergen extracts (allergens and quality) and dose schedules.
3. Due to this clinical and/or methodological diversity, we might reach “statistical heterogeneity” which unavoidably leads to wrong interpretations and clinical conclusions.

Real-world data

RWD definition

RWD is “data used for decision-making that are not collected in conventional RCTs” which “is obtained by any non-interventional methodology that describe what is happening in normal clinical practice.” [10, 11].

RWD includes information on health care that is derived from multiple sources outside typical clinical research settings like patient’s surveys, medical claims and observational cohort studies as opposed to data collected in an experimental setting such as RCTs [10, 11].

RWD information originated from electronic health records (EHRs), claims and billing activities, product and disease registries, datasets, proxy clinical data, etc.

RWE

RWE refers to real-world data that has been properly analysed leading us to be used as evidence.

Quality evaluation of RWD

Historical and still current systems appraise the quality of evidence-positioning RCTs on top of the pyramid and observational studies at the bottom, just above the “no evidence” level (i.e. expert).

Clinical guidelines from outstanding organizations worldwide [6, 7, 12–14] are now incorporating and implementing the Grading of Recommendations, Assessment, Development and Evaluation (GRADE), which still grant RCTs as high-quality evidence and observational studies as low-quality evidence but offer a distinctive and highly valuable opportunity to upgrade or downgrade these scores based on the detailed methodological characteristics of the studies.

A new user-friendly quality appraisal tool called RELEVANT (REal Life Evidence Assessment Tool) was developed and validated to assess quality standards in respiratory real-life studies [15•, 16••]. This tool comprises 21 quality sub-items (11 primary; 10 secondary) across seven core quality domains.

The quality of RCTs can be weakened through poorly detailed design and execution, inconsistency, complexity, reporting bias and inaccuracy. This mainly applies to old and small studies included in various SRs and MA in which poor quality non-standardized AIT products, no validated outcomes and inconsistent dose regimens have been included.

On the other hand, the quality of observational studies can be hoisted and reinforced through:

1. A proper study design with a priori registration
2. The use of robust methods of handling potential sources of bias (such as selection bias, information bias, detection bias, recall bias)
3. Collecting every relevant information that may influence the study outcomes
4. Establishing an interim analysis that allows detecting failures in the development of the study
5. Defining simple and real-life patients and inclusion criteria, which should include obesity, smoking and other co-morbidities
6. Limiting exclusion criteria (as compared with numerous in RCTs)
7. Clearly predefined study endpoints
8. Statistical analysis well defined a priori (statistical plan analysis)

Evidence-based medicine and real-world data in allergen immunotherapy

In the development of valid and usable clinical guidelines for AIT, some principles are fundamental:

1. The need for sufficient resources in terms of people with a wide range of skills, including expert clinicians, health services researchers, and group process leaders and financial support
2. A proper and up-to-date SR of the evidence should be at the heart of every guideline. Analysis and interpretation of this information should be used in a comprehensive and complementary manner when analysing data from AIT studies, which—in general—contain a large clinical and methodological heterogeneity.
3. The group assembled to interpret the evidence into a guideline should be multidisciplinary, including allergists, ENTs, paediatricians, respiratory physicians, nurses, patient's representatives, regulatory advisors, epidemiologists, statisticians and industry representatives. Each of them will contribute to different but complementary perspectives. This group should

include practising clinicians accustomed to the daily prescription and use of AIT (SCIT and SLIT). Academics with low clinical activities, researchers or doctor-politicians in the field of medicine and AIT should not provide clinical recommendations as they are not “experts” in the field.

Currently, we need to evaluate the efficacy and safety of AIT products in a more balanced, careful and realistic manner:

1. Analysing the results from product clinical development programmes in a comprehensive, critical and objective manner. Although data generated from RCTs is considered to be a trusted standard for assessing AIT safety and efficacy, we have to consider that patients participating in RCTs are carefully selected by clinical criteria inclusion. Therefore, analyses are needed to know the effect of AIT when this is given to different populations, different severity conditions that require other medications (interactions, side effects), as well as a long-term effect.
2. Incorporating the results of well-conducted observational non-interventional studies: data from real-life settings and clinical practice

EBM and AIT

During the last three decades, multiple SRs and MA on the effect and safety of SCIT and mainly SLIT have been performed worldwide. Most of them give a very positive outcome of efficacy for AIT compared with placebo or pharmacotherapy.

However, the medical community has “misused” the value of SRs and MA producing poor quality reviews, lacking rigorous methodological search and design issues. Health agencies are using RCT results for marketing authorization, while using other sources of data, including RWD, for pricing and reimbursement.

Some of these poor-quality SRs have included:

1. Old studies with “experimental” AIT products that never reached the registration
2. Studies with controversial clinical design
3. Studies with small population size
4. Mixed patients in the same protocol (e.g., children and adults)
5. Outcomes that were not validated
6. Therapeutic dosages and major allergen protein contents that were not properly documented
7. Poor quality or not standardized AIT products
8. Large variation in the duration of the trials, either too short or too long
9. Not comparable treatment schedules
10. Severity of disease that was not always consistent

From some of these careless SRs, data was used to perform MA. Therefore, the interpretation of their results should be critically evaluated. We have long ago considered that due to this high clinical and methodological heterogeneity

among studies, the results from some SRs and MA should be viewed with caution [3••, 8••].

AIT EBM is product specific

Considering the limitations provided by SRs and MA of AIT studies in terms of the high rate of clinical and methodological heterogeneity, the concept of “class effect” should not be used. Instead, we have to review the EBM of AIT as “product specific” [17•].

We need to be fair and objective. We must give the value and weight to those AIT products that have been thoroughly assessed and have properly document their efficacy and safety via a proper clinical development programme.

Each AIT product needs to be evaluated individually, based on its comprehensible study results, to justify efficacy and specific claims on sustained and disease-modifying effects per allergen and targeted patient group (children vs. adults, allergic rhinitis vs. asthma) [17•].

Moreover, at this time of clinical evolution and technology, we need to evaluate the results of the registered product not only in its context of RCTs, which do not entirely reflect real-life settings. We must consider current issues in the general population such as co-morbidity, including tobacco smoke and obesity, cost of the product, local health economic limitation, education level of the patient, proper identification of patients receiving AIT treatment in terms of disease severity and disease duration prior starting AIT. This information will be provided by well-designed RWD studies.

RWD and AIT

Real-world data provides “complementary” information to clinicians, researchers, industry, regulatory agencies and public health decision makers on the “effectiveness” and safety profile of AIT in real-life practice.

Proper well-designed studies need to be conducted to evaluate the role of RWD in AIT (Table 2).

Suggestions for these properly designed RWD studies in AIT are:

1. Combined retrospective with prospective data or follow-up
2. Aims clearly defined in the protocol
3. Transparent and well-standardized system for data collection
4. To have a targeted population (e.g. adults or children)
5. Sample size/power needs to be pre-specified.
6. To have a clear, correct and accepted disease diagnosis
7. To have a clear, correct and accepted disease severity
8. To have access to a validated and/or controlled proxies
9. To have clear primary realistic outcomes defined
10. To have a priori statistical analyses proposal
11. To have knowledge of the respective healthcare system
12. Interpretation of the collected data needs to be done in the context of the corresponding geographical and demographic real-life settings.

Some recent publications are fulfilling these requirements. A recent retrospective analysis of a German longitudinal prescription database evaluated the

Table 2. Weaknesses and strengths of using RWD in AIT

Weaknesses	Strengths
• Some regulatory and academic groups do not recognize RWD as evidence for AIT efficacy • Clinical information via proxies (e.g. use of asthma and allergic rhinitis prescription data) • Reimbursed drugs only • Widely differences of AIT products portfolio and their use, which complicated further comparisons • Quality of real-world databases from country to country is mixed. One database does not cover all the different settings that play a role in medical treatment.	• Reflects clinical practice and use of AIT (effectiveness, that is, how it works in actual practice) • More comprehensive picture of efficacy and effectiveness • Answers questions important to payers • Nationwide representative large cohorts • Comparison of AIT vs. standard of care • Not strict inclusion and exclusion criteria, making the study population more realistic, the better representative of the usual practice • Allow to identify use AIT off-label or in risky situations • Improved methodology and design: ○ Well-designed control groups ○ Matched control groups ○ Sophistication of scientific methods are increasing and will allow valid conclusions from RWD • Different formulation tested with the same methodology • Longitudinal data allowing patient follow-up over time • Less time-consuming and less expensive • Data available allowing long-term effectiveness assessment

progression of allergic rhinitis (AR) $\pm$ allergic asthma (AA) in patients receiving grass pollen SLIT tablets ($n = 2851$) compared with a control group not having received AIT ($n = 71,275$) [18•]. The authors described the real-world treatment of AR patients with grass pollen SLIT tablets to be associated with slower AR progression, less frequent AA onset and slower AA progression.

In a retrospective real-world analysis, prescription fulfilment data were gathered from French retail pharmacies between 01 March 2012 and 31 December 2016. Using linear regression analyses, patients having received at least two prescriptions of grass pollen SLIT tablets ($n = 1099$) over at least two successive years were compared with controls ($n = 27,475$). Authors found that the prescription of grass pollen SLIT tablets reduced the dispensing of AR and asthma medications in real life [19•].

Using RWD from a retrospective (1997–2009) Florida Medicaid claims analysis, Hankin et al. [20] identified that patients with newly diagnosed AR initiating AIT incurred significantly lower health care costs than matched control subjects beginning 3 months after AIT initiation and continuing throughout the 18-month follow-up period. Also, they observed that the significant cost benefits achieved by children with AR diagnoses who initiated AIT were also observed for adults with AR diagnoses who initiated AIT [20].

EBM and RWD in AIT clinical guidelines

The use of EBM and RWD in AIT should be complementary.

Once any product for AIT has completed its clinical development programme and reaches its pharmaceutical registration, constructive criticism and

objective analysis of its efficacy and safety profile, what is missed should be conducted by a multidisciplinary group of experts in the field of AIT. Future data on the effectiveness, safety, interactions and long-term effect of that AIT product should be sought by RWD analysis. These combined data will provide a clear visualization of the role of the AIT product in terms of disease control, the severity of symptoms and their progression and the possible preventive effect.

Guideline developers should use explicit evidence on AIT products. Data from both sources, EBM (obtained from RCTs and SRs) and RWD, should be critically analysed by a panel of experts that includes practicing clinicians and academics with strong AIT clinical and development experience; this might include allergists, ENTs surgeons, paediatricians, respiratory doctors, general practitioners, nurses, patient's representatives, regulatory authorities, statisticians and industry. This exhaustive unbiased analysis will provide the background for future recommendations for clinical practice and possible future guidelines.

When preparing clinical guidelines for AIT, we must also consider all geographical, demographic, cultural, political and socio-economic differences which need to be included in the clinical recommendations.

Guideline developers should not provide "general" statements on AIT as "class effect". This is incorrect and misleading; guidelines should be based on "specific AIT product" EBM and RWD.

The "absence" of evidence does not indicate "negative" evidence or the "evidence of no effect".

When clinical recommendations cannot be made based on EBM, due to the poor quality of the studies, we should consider integrating evidence from well-conducted RWD studies, especially for named patient products (NPP) that may provide a broader picture of intervention effectiveness and realistic treatment outcomes.

NPP is an allergen product, prepared with a specific reference number in accordance with a prescription for an individual patient, identified by the name of this patient and the reference number and delivered after control of consistency with previous treatments [21].

Data and guidelines generated from AIT studies should be evaluated by validated methods of grading the quality of evidence, such as GRADE or RELEVANT. The preparation of clinical recommendations must include a specific panel of multidisciplinary experts, all of them with strong and respected medical experience in the clinical practice of AIT.

Conclusion

We are now in a new era of evaluation of the evidence for any therapeutic intervention. AIT is already in this active process. Concepts are changing due to the development of new tools for the assessment of the quality of clinical data generated by EBM and RWD.

We must be "inclusive" and "critical" in our approach to evidence-based data. Clinical and methodological heterogeneity provides a limitation to EBM based on SRs and MA, while poorly designed RWD lose its value when poor-quality real-life studies are conducted.

Guideline development and/or decision-making in clinical practice needs to be based on objective criteria provided by well-conducted clinical programmes of a specific AIT product and complemented by its effectiveness and safety profile in real-life settings.

Compliance with ethical standards

Conflict of interest

Dr. Demoly reports personal fees from ALK, personal fees from Stallergènes Greer, personal fees from Iqvia, personal fees from Chiesi, personal fees from AstraZeneca, personal fees from ThermoFisher Scientific, personal fees from Sanofi-Regeneron, personal fees from Ménarini, personal fees from Bausch&Lomb and personal fees from Novartis, outside the submitted work.

Prof Dr. Moisés A. Calderon has received an honorarium as speaker from AKL-Abello, AKL-USA, ALK-Canda, Stallergenes Greer and HAL-Allergy and as an advisory board member from ALK-Abello, Stallergenes Greer, HAL-Allergy and ASIT-Biotech.

Dr. Rico has nothing to disclose.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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