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Underuse of allergen immunotherapy: a call to action

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Key points

- Allergen immunotherapy (AIT) is a disease-modifying treatment with long-term effects that persist after its discontinuation.
- Clinical guidelines should promote the earlier use of AIT in the disease management strategy (treatment algorithm).
- In the long term, AIT is more cost-effective than pharmacotherapy.
- Next-generation healthcare guidelines should integrate real-world evidence (RWE) into evidence-based medicine (EBM).
- Well-designed AIT registries, with pre-registered protocols, can serve as a valuable source of reliable real-world data (RWD).
- Increasing AIT use in clinical practice will provide lasting health benefits for an ever-increasing number of patients and substantial economic advantages for both individuals and the broader community.

Despite its proven effectiveness in treating allergic conditions, allergen immunotherapy (AIT) remains significantly underevaluated in clinical practice. On the contrary, there is a scientific interest in AIT research with more than doubled number of manuscripts published in the last decade respect to the previous years. This gap limits its potential to improve patient outcomes and advance our understanding of allergy management. To address this issue, healthcare professionals, researchers, and policymakers must prioritize comprehensive evaluation of AIT. Increased investment in clinical trials, real-world studies, and education will help clarify its long-term benefits, safety profile, and optimal application across diverse patient populations. Collaborative efforts will ensure that AIT achieves its full potential, ultimately enhancing the quality of life for those affected by allergies. Estimates suggest a significant gap between

eligible and treated patients for AIT, with one study in Italy showing only about 33.1% of eligible patients were proposed AIT, but only 29% of them accepted the treatment [1], and a US study indicating that just 2–9% of eligible allergic rhinitis patients received it in 2015 [2]. A national audit in UK revealed only 1% of eligible children receiving AIT for severe allergic rhinitis [3]. In general, there are challenges in the prescription of AIT as underlined in the EAACI AIT guidelines [4]. These low percentages are often due to a lack of awareness among healthcare providers and patients, costs, and concerns about treatment duration or efficacy.

The paradox is that in many countries there is a reduction in the prescription of AIT [5] with the increase in prevalence of patients suffering from allergies, despite there are compelling evidence of the efficacy of AIT in the management of allergies, offering far more than mere symptom relief: It modifies the course of the disease [6, 7]. It has been demonstrated that AIT induces allergen-specific tolerance after a treatment course of 3 years [8] that provides clinical benefit for years after its discontinuation. It ameliorates the patient's quality of life and improves work/school productivity [9]. AIT efficacy has been demonstrated for allergic rhinitis and asthma [10–12], both in children [13, 14] and in adults [12, 15] and in the elderly [16, 17], both with the sublingual or the injective administration [4], without relevant side effects when correctly used by specialists or trained physicians [10, 18–20]. Following the most recent diagnostic possibilities (component resolved diagnosis), choosing the route of administration (sublingual, injectable), type of medicine (tablets, drops), and administration schedule, considering patient possibilities and agreement, AIT is a prototype of precision/personalized medicine [21, 22].

The mechanisms of AIT are extensively studied, it retrains the immune system, shifting it away from a hypersensitive state toward one of tolerance. AIT acts on both innate and adaptive immune responses that contribute to allergic inflammation. AIT favors the generation of tolerogenic DCs producing high levels of IL-10, consequently polarizing and expanding different functional subsets of allergen-specific Tregs and Bregs. Regulatory cells suppress the activity of different cell types (mast cells, basophils, eosinophils, ILC2s, Th2 cells, DCs, and B cells) and favor the production of IgG4 blocking antibody by the secretion of IL-10 and of IgA blocking antibody by TGF-beta [23–27]. Changes in innate immune cell composition and diversity, which normalize to non-allergic levels after AIT, indicate that trained immunity plays a key role in establishing long-lasting immune tolerance to allergens and preventing new allergic sensitizations. Trained immunity allows innate immune cells to develop a type of non-specific "memory" and enhanced responsiveness, leading to a more effective and healthy immune response to allergens [28, 29]. Of note that changes in the immunologic profile, in particular the increase in Treg cells correlates with clinical improvement [30, 31]. Over time, these changes promote immune tolerance, effectively "re-educating" the body to encounter the allergen without triggering inflammation. Clinically, this process not only reduces the severity and frequency of symptoms but also reduces the need for medications such as antihistamines and corticosteroids [32, 33]. One of the most compelling advantages of AIT is its potential for long-lasting benefit [34]. Unlike conventional pharmacotherapy, which primarily targets symptoms, AIT addresses the underlying cause of allergic disease, and after completing a full course, many patients experience sustained symptom relief that can persist for years, even after treatment cessation. Furthermore, it reduces the likelihood of developing new sensitivities and can even prevent the progression from allergic rhinitis to asthma, especially in children [35, 36].

Recently, it has been introduced in allergology the concept of disease remission after treatment. There is a definition of remission for asthma, but there is no consensus on the definition of remission in allergic rhinitis. In any case, we can assume that remission could be identified as a long symptom and medication free period after cessation of AIT. In this respect, there are studies showing variable percentages of patients with long lasting complete or partial asthma/rhinitis remission after a full course of AIT. This long-term effect is a unique feature of AIT compared to other treatments, since after stopping these drugs, a disease relapse is observed [37–40].

Despite increasing awareness of allergic diseases worldwide and the increasing recognition of the benefits of AIT, its integration into standard care protocols remains inconsistent, and there remains a notable gap between evidence and implementation in routine care. In UK, the registry for immunotherapy

showed disparities in access to allergy treatments, which are linked to socio-economic and ethnic factors affecting specialty care availability [41]. Only a very small percentage of patients who would benefit from the therapeutic effects of AIT are offered this option [1].

Reasons for the lack of use of AIT are many.

Many clinicians may be hesitant to recommend or initiate AIT due to limited training, perceived complexities in administration, or uncertainty about long-term outcomes. Limited training seems to be the most important problem for doctors, in particular, general practitioners. The EAACI Allergy Educational Needs in Primary Care Pediatricians Task Force conducted a survey across Europe showing that in medium, only 50% of doctors received allergy teaching and training as undergraduates [42], confirming previous studies investigating current allergy educational needs in primary care [43]. The data is of particular interest, showing that almost 50% of general practitioners cannot correctly diagnose and manage allergic conditions. In this condition also the correct referral to an allergology specialist is highly unlikely.

In every published manuscript concerning AIT prescription, there is a request for clear and indicative guidelines for both general practitioners and specialists. In this respect, the indication on AIT prescription by EAACI guidelines published in 2018 [13] leaves more than a few doubts. The guidelines stated: AIT should be prescribed in patients with oculorhinitis uncontrolled while using pharmacotherapy, eventually adding nasal antihistamine/steroid, ocular antihistamine/cromoglicate and montelukast to antihistamines. That means: Some patients should take all these medicines forever if symptoms are controlled? What is the benefit for the patient, the healthcare system, and the community? A part of the possible side effects of a long use of these drugs, the guidelines recognize the effectiveness of AIT and stated that "*Several health economics studies that include cost-effectiveness and cost utility calculations have demonstrated that SCIT and SLIT are economically advantageous to pharmacotherapy.*" [44–47]. AIT is generally cost-effective for managing allergic rhinitis and asthma compared to standard drug treatment alone, even considering its higher upfront costs, and the actual economic benefit is likely underestimated because most studies do not fully capture its long-term preventive effects [48–51]. Therefore, the use of AIT offers long lasting health benefits for patients and economic advantages for patients and community when correctly prescribed for oculorhinitis and/or asthma with demonstrated allergic etiology. AIT is a therapeutic option that appears to be even more valid in children, since the long-term and preventive effects on further sensitizations and the evolution from rhinitis to asthma are observed especially in younger age groups [52–54].

Addressing these obstacles requires implementing targeted educational initiatives to boost health literacy, creating streamlined user-friendly guidelines, and policy changes to ensure equitable access for all patients.

In EU, most of the authorized allergen products have national marketing authorizations and several are distributed as named patient product under the Article 5 of the Directive 2001/83/EC. However, these products frequently lack sufficient documentation regarding their quality, safety and efficacy, which raises regulatory concerns. Recently, guidance has been published to harmonize the regulatory requirements for allergen products [55–57]. However, the primary challenge for allergen manufacturers entering a registration pathway is represented by the cost too high for many small and medium enterprises and for products with a very small market. International guidelines suggest that double-blind, placebo-controlled trials, the gold standard to demonstrate efficacy and safety of a medicine, should have a duration of 3 years of treatment and two years of follow-up to demonstrate a sustained effect for AIT products [58].

It is likely indispensable to use a different experimental approach, and there are efforts in this way [59]. For example, an interesting three-stage design for AIT trials has been proposed in which the placebo group in Stage 1 crosses over to receive active treatment in Stage 2 (so preventing keeping the control arm on placebo for the entire duration of the trial) and AIT is discontinued in Stage 3 [60].

Many authors suggest the possibility of using real-world data (RWD) to sustain the efficacy and safety of AIT [34, 61]. Recent studies have shown the integration of real-world evidence (RWE) in marketing authorization applications over the past years, essentially for rare diseases and in the case of precision medicine [62]. In a review [63], the utility of RWE for the long-term effect of AIT has been reported,

showing positive results. However, it is stressed that it will probably take some more years, more data and, first of all, a better methodology for RWE to be supportive for regulatory purposes.

At the end of 2023 FDA published a guidance for industry, "Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products" stating that a registry can contribute to the decision of the regulatory agency, when some characteristics are met, first of all, the reliability of the data source [64]. Currently, the possibility of utilizing RWE to support regulatory decision making for AIT is in discussion among regulators, allergology specialists, and allergen manufacturers. In October 2023, the 2nd European Academy of Allergy & Clinical Immunology/Respiratory Effectiveness Group (EAACI/REG) Workshop was held in Rome, Italy, with the thematic issue: How to integrate RWE in evidence-based medicine (EBM). The conclusion of the meeting evidenced that "*The integration of RWE into evidence-based decision-making has become a practical necessity rather than just a theoretical concept. The workshop consensus concludes that high-quality RWE, when generated and interpreted with rigorous methods, can effectively supplement or sometimes replace data from randomized controlled trials (RCTs).*" [65]. Next-generation health guidelines are increasingly leveraging RWD to enhance EBM by providing insights into drug effectiveness in broader, more diverse patient populations than traditional clinical trials. RCTs primarily measure a drug's efficacy (how well it works in ideal conditions), while RWD provides evidence of its effectiveness (how well it works in routine clinical practice). RCTs often enroll a small, highly selected patient group, while RWD captures data from a larger, more diverse population, including individuals with multiple comorbidities who are excluded from trials. RWD helps fill the gaps left by RCTs by providing data on long-term outcomes, safety, and outcomes in specific subpopulations not studied in controlled trials [66].

EMA in February 25 published the "Real-world evidence framework to support EU regulatory decision-making" based on the 3rd report on the experience gained with regulator-led studies from February 2024 to February 2025. The executive summary concluded: "*This report shows that thanks to the work done over the last 4 years the use of RWE is now enabled, and its value continues to be established across the full range of regulatory use cases.*" [67].

While RWD is valuable, potential biases and the need to ensure data quality and integrity are crucial considerations. Concerns about RWE included a lack of a prespecified study design and analysis plan and incomplete or inaccurate data collection, missing confounding variables, insufficient statistical methods to account for RWD's complexities, and a lack of consensus on methodologies.

Disease registries can overcome these issues. Registries collect RWD by prospectively gathering longitudinal clinical and other information on defined patient populations over time, in a real-world setting, offering valuable insights into disease progression, product safety and effectiveness, and providing real-world context for designing clinical trials. These organized systems capture detailed, standardized data that reflects actual clinical practice, providing a broader and more diverse patient view than controlled trials can offer. Registries can enroll a larger and more diverse patient population than clinical trials, which helps to understand outcomes in various subgroups and underrepresented populations. They gather specific, detailed clinical and demographic data that can be essential for research and regulatory purposes [68]. In Italy, a registry for AIT was established in 2024 by the Italian Society of Allergy, Asthma and Clinical Immunology and by the Italian Society of Pediatric Allergy and Clinical Immunology. The protocol was published in 2024 [69] and registered on ClinicalTrials.gov ID NCT06499480. It is a prospective multicenter observational registry of patients suffering from conjunctivitis, rhinitis, and/or allergic asthma eligible for and treated with AIT, with prespecified study design, clear objectives, and analysis plan. A discussion has been initiated with the Italian Medicines Agency (AIFA) for its use as data source for RWD/RWE to be applied for regulatory purposes.

All allergologists and allergy manufacturers are prompted to participate in this endeavor, to rapidly reach the critical number of patients treated and to maintain over time a complete set of data.

As research and education around AIT continue to grow, collaboration among healthcare professionals, researchers, industry, and policymakers will be critical to unlocking its full potential for individuals and communities.

Abbreviations

AIT: allergen immunotherapy

EBM: evidence-based medicine

RCTs: randomized controlled trials

RWD: real-world data

RWE: real-world evidence

Declarations

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Mario Di Gioacchino is the Past-President of the Italian Society of Allergy, Asthma and Clinical Immunology. Lorenzo Cosmi is the President of the Italian Society of Allergy, Asthma and Clinical Immunology Foundation. Sebastiano Gangemi is the President-elect of the Italian Society of Allergy, Asthma and Clinical Immunology. Vincenzo Patella is the President of the Italian Society of Allergy, Asthma and Clinical Immunology. Giorgio Walter Canonica is General Executive Manager of the Italian Society of Allergy, Asthma and Clinical Immunology.

Author contributions

MDG, LC, SG, VP, GWC: Writing—original draft, Writing—review & editing. All authors read and approved the submitted version.

Conflicts of interest

Mario Di Gioacchino and Giorgio Walter Canonica are the Editors-in-Chief of Exploration of Asthma & Allergy. Vincenzo Patella is the Editorial Board Member and Guest Editor of Exploration of Asthma & Allergy. Lorenzo Cosmi and Sebastiano Gangemi declare that they have no conflicts of interest.

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