# **Mini Review**

# The prescriptive paradox of allergen immunotherapy for respiratory allergic diseases

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#### **SUMMARY**

Allergy immunotherapy (AIT) is an effective, safe, and cost-efficient treatment for allergic rhinitis and asthma. Nevertheless, the prescription of AIT is paradoxically low and is progressively decreasing in Italy. Barriers exist, including the lack of guidelines for primary care physicians (PCPs) and specialists, insufficient agreed-upon pathways between specialists and PCPs, and complexities in the prescriptive process. It is necessary to rethink the approach to this issue through a collaborative and integrated effort among all players involved in improving accessibility and utilization of AIT for the treatment of allergic respiratory diseases.

**KEYWORDS:** Allergy immunotherapy (AIT), Italian Drug Agency (IDA), European Medicines Agency (EMA), Primary Care Professional (PCP), Subcutaneous immunotherapy (SCIT), Sublingual Immunotherapy (SLIT)

# **INTRODUCTION**

AIT for the treatment of allergic respiratory diseases has been used in practice for more than 100 years. Typically, either subcutaneous AIT (SCIT) injections or sublingual AIT (SLIT) are used <sup>1-3</sup>. We assessed the evidence on the effectiveness, cost-effectiveness and safety of AIT. AIT involves the administration of allergens to shift the immune response from immediate hypersensitivity towards tolerance <sup>4</sup>.

Extensive research on AIT conducted over the last few decades has confirmed its efficacy, safety, and cost efficiency in the treatment of allergic rhinitis and asthma. Recent international documents recommend AIT in adults as well as adolescents and children over 6 years of age <sup>5-7</sup>. Moreover, AIT has been shown to effectively reduce the risk of exacerbations and lower

respiratory tract infections in both seasonal and perennial allergic asthma <sup>8</sup>. Nevertheless, the prescription of AIT is paradoxically low and is progressively decreasing in

Italy. This suggests that barriers to its implementation likely exist.

# **BARRIERS TO AIT**

An analysis of the current provision of allergen immunotherapy in Europe <sup>9</sup> has identified several gaps and deficiencies. While almost all countries (92%) report the availability of AIT, guidelines for PCPs and specialists, as well as agreed-upon pathways between these groups, are present in fewer than 50% of countries. Furthermore, reimbursement policies and the cost of AIT appear to be important barriers to its widespread adoption.

The issue of reimbursement for practitioners and patients needs to be addressed, as it may affect accessibility to AIT. These issues include costs related to travel and time lost from work. Some countries, such as Germany, Denmark, and the UK, provide more support for allergy care than others, such as Portugal, Malta, and Ireland <sup>10</sup>.

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This is an open access article distributed in accordance with the CC-BY-NC-ND (Creative Commons Attribution-Non-Commercial-NoDerivatives 4.0 International) license. The article can be used by giving appropriate credit and mentio-ning the license, but only for non-commercial purposes and only in the original version. For further information: https://creativecommons.org/ licenses/by-nc-nd/4.0/deed.en In Italy, AIT is offered free of charge (with a therapeutic plan) through the Italian National Health System (Sistema Sanitario Nazionale or SSN), but only for a few prescriptions identified by the Italian Drug Agency (Agenzia Italiana del Farmaco or AIFA). This selection aligns with the rigorous evaluation standards of the European Medicines Agency (EMA), which includes chemical, pharmacological, preclinical, and clinical studies.

# **IMPLEMENTATION OF AIT**

The implementation of AIT should involve the various actors in the prescriptive process, including specialists, general practitioners (GPs) and pediatricians, regulatory organizations, national health systems (NHS), scientific organizations, the political system, patient associations, and companies.

#### 1. Specialists

Specialists in allergy and immunology should be considered the primary actors in the prescription and surveillance of AIT. Since AIT requires specific theoretical and practical knowledge, periodic professional training should be organized by allergy scientific societies. This training should target specialists with a particular interest in allergic respiratory diseases, including pulmonologists, otolaryngologists, dermatologists, and PCPs.

Moreover, communication during AIT prescriptions should be improved to foster better understanding among patients (and their parents, when applicable). Clear explanations of the characteristics of AIT are essential to achieving a strong therapeutic alliance (Tab. I).

## 2. General Practitioners and Pediatricians (PCPs)

PCPs, including general practitioners and pediatricians, should collaborate with specialists in the management of AIT prescriptions. One of the greatest barriers perceived by PCPs working with AIT in Europe is suboptimal communication with specialists.

Enhanced dialogue between specialists and PCPs can improve knowledge and streamline treatment pathways at the local level. Currently, PCPs are not adequately trained to manage allergy patients.

Allergies are rarely featured in undergraduate medical curricula, and there is minimal allergy training in postgraduate primary care specialist programs. To address this gap, allergy and AIT training should be included in all undergraduate medical curricula as well as in postgraduate primary care specialist training programs. Moreover, vertically integrated care pathways to improve the delivery of AIT should be implemented<sup>9</sup>situational analysis.

In a study based on an online questionnaire regarding the behavior of 460 Italian family pediatricians in managing allergic diseases<sup>11</sup>, only 9 pediatricians declared a specific interest in allergy. However, 171 (37%) reported using AIT in some form, almost exclusively via the sublingual route. This indicates a notable interest within the category that could be appropriately addressed through postgraduate training.

## 3. Regulation and Acceptance of Allergen Products

In recent years, there have been significant changes in the allergen market, which have impacted the availability of allergen products. Within the EU, the regulation and acceptance of AIT products vary widely across regions. In Italy, AIFA considers two types of products for AIT: Named Patient Products (NPP) and authorized market products (Autorizzazione Immissione Commercio or AIC). AIC products for respiratory allergic diseases are widely available for grass, ragweed, and mite allergens.

NPPs are available upon specific prescription by any physician and are produced by several manufacturers. These products are fully paid for by patients in most Italian regions, with exceptions such as Lombardia, Val D'Aosta, Piemonte, Trentino Alto Adige, and Puglia.

## 4. National Health System (NHS)

In Italy, the NHS (or SSN) provides free AIC for grass pollen allergic rhinitis in children over 6 years old and adults in all regions. However, AIC for mite allergic rhinitis and asthma is currently available free of charge only in Tuscany and Trentino-Alto Adige. A therapeutic plan, drawn up by medical staff designated by NHS local health departments, is required for these prescriptions. Specialists outside the SSN can prescribe both AIC and NPP products, but the cost is

#### TABLE I. AIT for respiratory allergic diseases: What to explain to patients/parents.

AIT is not a vaccine but an antiallergic treatment.

It is a natural treatment (it uses the same allergic substance to obtain a protective immunologic response).

It is a safe treatment.

It is efficacious (reduces symptoms by about 40-50%).

It is also efficacious in reducing the risk of exacerbations and lower respiratory tract infections in both seasonal and perennial allergic asthma patients.

It is a long treatment (at least 3 years).

It is the only treatment that modifies the natural history of the allergic disease.

AIT: allergen immunotherapy.

entirely borne by patients. The use of AIT with NPP products in Italy is relatively low and has progressively decreased over the past two decades, from approximately 400,000 treatments in 2000 to about 100,000 in 2022. Data on AIC sales are not available but are likely low, as they are limited by spending ceilings defined by individual regions, difficult access to dedicated outpatient <sup>9</sup> clinics, and long waiting lists. This creates a prescriptive funnel for AICs, preventing most patients who need AIT from obtaining it free of charge. Therefore, there is a need to increase the number of medical staff authorized to prescribe AIC products for AIT covered by the NHS.

## 5. Scientific Societies

Although recommendations for competency in allergy training and pocket guides for allergen-specific immunotherapy for allergic rhinitis and asthma have been published by many scientific societies <sup>12-14</sup>, guidelines for PCPs and specialists, as well as agreed-upon pathways between them, exist in fewer than 50% of European countries<sup>9</sup>.

The main scientific societies involved in AIT for adults and children in Italy – Società Italiana di Allergologia e Immunologia Clinica (SIAIC), Associazione Allergologi e Immunologi Italiani Territoriali e Ospedalieri (AAIITO), and Società Italiana Allergologia Immunologia Pediatrica (SIAIP) – have, in recent years, published consensus documents on the practical aspects of AIT for adults <sup>15</sup> and for children <sup>16</sup>.

However, there is a pressing need to strengthen the connection between scientific organizations, PCPs, and patient associations to synergistically promote a correct, evidence-based understanding of allergy care. This effort should focus on identifying shared diagnostic-therapeutic pathways (assessment, prescription, treatment) and establishing training courses with the active collaboration of PCP associations and patient associations. In this regard, AllergicaMente (https://www.allergicamente.it/allergie/ respiratorie)<sup>17</sup>, an initiative of the AAIITO, offers clear and simple recommendations to facilitate the recognition, diagnosis, and treatment of allergic diseases, including AIT.

Such initiatives must be implemented at the regional level, considering the organization of the Italian NHS and the fact that Italian scientific societies have regional coordinators. At a local level, priority should be given to practical approaches.

#### 6. Patient associations

There are many patient associations in Italy for those suffering from allergic respiratory diseases,<sup>18</sup> but none clearly support the use of AIT in the treatment of allergic rhinitis and asthma. A link between these associations and the AAIITO site AllergicaMente may be useful to increase patients' knowledge and provide appropriate recommendations for the diagnosis and treatment of allergic respiratory diseases. Staunch support for patient associations is fundamental to increase the use of AIT to treat allergy patients.

## 7. Companies

In Italy, companies that sell products related to AIT (ALK-Abello, Stallergenes, Lofarma, Allergy Therapeutics, Anallergo, HAL Allergy,

Roxall) were once part of an association called Assobiomedica, but that is no longer the case. Nevertheless, there is a need for a synergistic effort among companies to promote the use of AIT.

#### 8. Press and social networks

Proper information on AIT could be amplified by means of the press and social networks, especially networks connected to patient associations.

#### 9. Political system

The involvement of the political system is fundamental for the identification of standards relating to the number of allergy structures/ services per capita and the homogenization of the prescription and free availability of AIT throughout the nation. For this purpose, a parliamentary intergroup on respiratory allergies <sup>19</sup>, which includes representatives of the presidents of SIAIC, AAIITO, and SIAIP, proposes to "guarantee full access to the use of more advanced therapies for the treatment of respiratory allergies, including desensitizing therapies and NPPs (Named Patient Products), regulated by art. 5 of law n.94/1998, in line with the principles of therapeutic appropriateness, sustainability for the national health system, and equal access to care in all regions, eliminating all sorts of inequities."

# **CONCLUSIONS**

In conclusion, it is evident that there is a prescriptive AIT paradox in the treatment of respiratory allergic diseases.Despite a growing body of evidence-based research produced over recent years on its efficacy and safety, the rate of prescriptions for AIT is progressively decreasing. It is evident that whatever has been done before now to promote AIT has not been effective. It is necessary to rethink the existing approach through a collaborative and integrated effort involving all players involved in the utilization of AIT (Fig. 1).



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## Author's contribution

EN: supervision, writing-original draft, writing-review and editing; SB: review and editing; FM: review and editing.

#### References

- <sup>1</sup> Dhami S, Nurmatov U, Arasi S, et al. Allergen immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis. Allergy 2017;72:1597-1631. https://doi.org/10.1111/all.13201
- <sup>2</sup> Alvaro-Lozano M, Akdis CA, Akdis M, et al. EAACI Allergen Immunotherapy User's Guide. Pediatr Allergy Immunol 2020;31(Suppl 25):1-101. https://doi. org/10.1111/pai.13189
- <sup>3</sup> Dhami S, Kakourou A, Asamoah F, et al. Allergen immunotherapy for allergic asthma: A systematic review and meta-analysis. Allergy 2017;72:1825-1848. https://doi.org/10.1111/all.13208
- <sup>4</sup> Jutel M, Agache I, Bonini S, et al. International Consensus on Allergen ImmunotherapyII: Mechanisms, standardization, and pharmacoeconomics. J Allergy Clin Immunol 2016;137:358-368. https://doi.org/10.1016/j. jaci.2015.12.1300
- <sup>5</sup> Levy ML, Bacharier LB, Bateman E, et al. Key recommendations for primary care from the 2022 Global Initiative for Asthma (GINA) update. NPJ Prim Care Respir Med 2023;33:7. https://doi.org/10.1038/s41533-023-00330-1
- <sup>6</sup> Bousquet J, Pfaar O, Togias A, et al. 2019 ARIA Care pathways for allergen immunotherapy. Allergy 2019;74:2087-2102. https://doi.org/10.1111/ all.13805

- <sup>7</sup> Cox LS, Murphey A, Hankin C. The Cost-Effectiveness of Allergen Immunotherapy Compared with Pharmacotherapy for Treatment of Allergic Rhinitis and Asthma. Immunol Allergy Clin North Am 2020;40:69-85. https://doi.org/10.1016/j.iac.2019.09.003
- <sup>8</sup> Woehlk C, Von Bülow A, Ghanizada M, et al. Allergen immunotherapy effectively reduces the risk of exacerbations and lower respiratory tract infections in both seasonal and perennial allergic asthma: a nationwide epidemiological study. Eur Respir J 2022;60:2200446. https://doi. org/10.1183/13993003.00446-2022
- <sup>9</sup> Ryan D, Gerth van Wijk R, Angier E, et al. Challenges in the implementation of the EAACI AIT guidelines: A situational analysis of current provision of allergen immunotherapy. Allergy 2018;73:827-836. https://doi.org/10.1111/ all.13264
- <sup>10</sup> Bonertz A, Roberts GC, Hoefnagel M, et al. Challenges in the implementation of EAACI guidelines on allergen immunotherapy: a global perspective on the regulation of allergen products. Allergy 2018;73:64-76. https://doi.org/10.1111/all.13266
- <sup>11</sup> Cerimoniale G. Indagine epidemiologica sulla gestione delle patologie allergiche da parte del pediatra di famiglia. Il Medico Pediatra 2017;4-8.
- Potter PC, Warner JO, Pawankar R, et al. Recommendations for competency in allergy training for undergraduates qualifying as medical practitioners: a position paper of the World Allergy Organization. Curr Allergy Clin Immunol 2011;24:125-129.
- <sup>13</sup> Zuberbier T, Bachert C, Bousquet PJ, et al. GA<sup>2</sup> LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma. Allergy 2010;65:1525-1530. https://doi.org/10.1111/j.1398-9995.2010.02474.x
- <sup>14</sup> Roberts G, Pfaar O, Akdis CA, et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. Allergy 2018;73:765-798. https://doi.org/10.1111/all.13317
- <sup>15</sup> Musarra A, Bilò MB, Canonica GW, et al. Consensus on allergen specific immunotherapy. Eur Ann Allergy Clin Immunol 2013;45 (Suppl 3):1-49.
- Payno G, Bernardini R, Terracciano L, et al. Immunoterapia con allergeni (AIT): Consensus della Società Italiana di Allergologia e Immunologia Pediatrica (SIAIP) per la pratica clinica in pediatria. Rivista di Immunologia e Allergologia Pediatrica 2015;(4 Suppl 4):1-19.
- <sup>17</sup> www.allergicamente.it/allergie/respiratorie
- <sup>18</sup> www.ripartiamo2021.org/sito/index.php/associazioni/32-allergamici
- <sup>19</sup> www.aaiito.it/news/intergruppo-parlamentare-sulle-allergie-respiratorie/