Review

Illustrative Case Series and Narrative Review of Therapeutic Failure of Immunotherapy for Allergic Rhinitis

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Abstract

This is a series of 4 cases (3 therapeutic failure and 1 early relapse) in adult patients treated with allergen immunotherapy (AIT) for allergic rhinitis (AR) in our immunotherapy clinic, which treats 110 new patients per year. AIT includes both subcutaneous and sublingual routes. The current national/international AIT recommendations and the literature have been searched to identify guidance for the optimal management of therapeutic failure of AIT in AR. There is scant information available to support clinicians when treatment failure and/or intolerable side effects occur. The importance is highlighted for developing the guidance and evidence base for the benefit of this patient subgroup. The potential strategies that clinicians have proposed are discussed in this article, though it is acknowledged that these are mostly not evidence-based.

Keywords

allergen, side effects, tolerability, desensitization, grass pollen

Introduction

Allergen immunotherapy (AIT) is a globally used superior treatment for allergic rhinitis (AR) and remains the only curative treatment. AIT includes both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). In addition to curative potential, AR may influence subsequent development of asthma in children with AR.[1,2] AIT is indicated for moderate/severe AR, when symptom control has not been achieved with allergen avoidance and/or pharmacological methods, and there is evidence of specific immunoglobulin E (IgE) to clinically relevant allergens.[3–6] Treatment is usually carried out for at least 3 years (can be 3–5 years, dependent on the duration of the maintenance period).[5–8] While there is greater experience with SCIT, it is well recognized that both SCIT and SLIT are effective in the treatment of AR.[9–12] Detailed systematic reviews and meta-analyses, including a limited number of studies directly comparing efficacy between SCIT and SLIT, concluded no major difference.[11–13]

However, even with careful patient selection, treatment failure may still occur. In our clinical practice, we observe a very small percentage of therapeutic failures with AIT. We have considered therapeutic failure as either inadequate symptomatic response or intolerable side effects, which are both well recognized.[14,15] This is a series of 4 cases (3 therapeutic failure and 1 early relapse) encountered in our AIT clinic, where patients are treated using either SCIT or SLIT protocols, depending on clinical evaluation and patient preference. All patients provided informed consent to be included. Assessment according to the National Health Service Health Research Authority definitions indicated that Research Ethics Committee approval was not required

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for this anonymized case series. We have provided a narrative review of current guidelines and the wider literature for pertinent advice on the optimum management of such clinical circumstances.

Case Studies

Case 1

A 33-year-old man of South Asian origin presented with a 2-year history of seasonal AR and asthma. His symptoms had not been controlled by antihistamines, montelukast, intranasal steroids, and cromoglicate eye drops. He had a medical history of intermittent asthma. Skin prick testing was positive for grass pollen with weal diameter 10 mm. Serum-specific IgE was also positive for a range of grasses (Cocksfoot >100 kUA/L, Meadow >100 kUA/L, Redtop >100 kUA/L, Rye 89.60 kUA/L, Timothy grass 76.80 kUA/L; Timothy grass components: Phl p 1 = 55.9, Phl p 2 = 26.1, Phl p 5 = 62.1, Phl p 6 = 18.4, Phl p 11 = 0.19, Phl p 12 Profilin <0.10 kUA/L).

He was subsequently commenced on SLIT with timothy grass (*Phleum pratense*) allergen extract 75 000 standardized quality units tablet (SQ-T; *Grazax®* oral lyophilisate) but developed mouth ulcers, tongue swelling, and numbness over the course of a few days after starting treatment. The mouth ulcers persisted for some time so *Grazax®* was discontinued. He was then started on grass pollen *Alutard SQ®* SCIT and progressed well through updosing and initial maintenance. He received maintenance injections at 100 000 standardized quality units (SQ-U) for 18 months when he had an anaphylactic reaction requiring adrenaline and admission. Consequently, the decision was taken to stop the *Alutard SQ®*. Subsequently, the patient was tried on *Staloral®* SLIT grass pollen mix commencing at 1 press of 100 index of reactivity (IR)/mL increasing gradually to 4 presses of 300 IR/mL solution, but he developed problematic oral swelling, and this product was discontinued. Preseasonal grass pollen SCIT with high-dose hypoallergenic aluminium hydroxide-adsorbed depot preparation modified with formaldehyde (*Allergovit®* 6-grasses allergoid) was then started as patient continued to be symptomatic. However, despite reaching the recommended maintenance dose of 6 000 therapeutic units, the patient did not have a clinical response, and a decision was taken not to proceed to year 2. He subsequently commenced *Pollinex® Quattro* SCIT (preseasonally) which contains a different adjuvant (L-tyrosine and MPL—monophosphoryl lipid A). As of year 1, he has had a reasonable response at the maximum recommended dose of 2000 standardized units (SUs). Another option considered, but kept in reserve, was to restart *Alutard SQ®* but aiming for a lower maintenance dose of 10 000 SQ-U in year 1, and 30 000 SQ-U in year 2. (The previous *Alutard SQ®* maintenance dose was 100 000 SQ-U.)

Case 2

A 39-year-old Caucasian man with seasonal AR since he was a teenager, presented with symptoms uncontrolled on antihistamines and intranasal steroids. Skin prick tests showed a positive grass pollen weal of 7 mm. Serum-specific IgE was also positive for a mixture of grass pollens (8.46 kUA/L) containing Cocksfoot, Meadow, Rye, Kentucky blue, and Timothy grass (Timothy grass components: Phl p 1 = 1.9 kUA/L, Phl p 5 = 1.7 kUA/L, Phl p12 Profilin <0.10 kUA/L). He was commenced on preseasonal *Pollinex®* grasses and rye SCIT, reaching a maintenance dose of 2000 SU. Unfortunately, there was no treatment response after 2 years. However, following a third year of SCIT with the same product, he eventually had improvement in his symptoms.

Case 3

A 31-year-old man resented with a 2-year history of severe seasonal AR, unresponsive to medical therapy with antihistamines, montelukast, intranasal steroids, and cromoglicate eye drops. Allergen-specific IgE was positive for a range of grass pollens (Cocksfoot >100 kUA/L, Meadow >100 kUA/L, Redtop >100 kUA/L, Rye >100 kUA/L, Timothy grass >100 kUA/L; Timothy grass components: Phl p 1 > 100, Phl p 2 = 24.2, Phl p 4 > 100, Phl p 5 > 100, Phl p 6 > 100, Phl p 11 = 2.90, Phl p12 Profilin = 0.5).

He was commenced on timothy grass (*Phleum pratense*) standardized allergen extract 75 000 SQ-T (*Grazax®*), but he developed problems with mouth swelling and so this had to be discontinued. The patient was then started on *Alutard SQ®* grass pollen SCIT. He tolerated this but despite 3 years of therapy reaching 100 000 SQ-U, only had marginal improvement in symptom control. *Pollinex® Quattro* was then started but with no response after 1 year of treatment.

Case 4

A 42-year-old Caucasian woman presented with severe seasonal AR symptoms not fully controlled despite oral antihistamines, nasal steroids, and antihistamine eye drops. She had a medical history of intermittent asthma and Crohn's disease. Skin prick testing showed a 10 mm wheal to grass pollen. Allergen-specific IgE was moderately positive for some grass pollens (Cocksfoot 2.2 kUA/L, Meadow 2.5 kUA/L, Redtop 1.91 kUA/L, Rye 1.71 kUA/L, Timothy grass 1.08 kUA/L; Timothy grass components: Phl p 1 = 1.4, Phl p 2 = 0.2, Phl p

4 = 0.5, Phl p 6 = 0.1, Phl p 11 = 0.35, Phl p 12 Profilin <0.10).

The patient completed 3 years of treatment with *Alutard SQ®* reaching 100 000 SQ-U with improved symptoms while on treatment. However, she had a relapse of her hay fever symptoms in the season immediately following discontinuation.

Discussion

Therapeutic failure can be considered as resulting from either inadequate clinical response or intolerable side effects.[14,15] The possible reasons for inadequate clinical response are summarized in Table 1. The current published guidelines and the medical literature (Pubmed, Cochrane Library, National Institute of Health, and Care Excellence) have been reviewed to look for guidance as to appropriate management when therapeutic failure arises. The current guidelines draw attention to the importance of correct patient selection, the type of allergen, and the product chosen for treatment. Table 2 provides a comparison of American, British, and European guidelines for the patient selection process for AIT administration and treatment failure.[16–20] The guidelines acknowledge that a minority of correctly selected patients fail to respond but provide no further support for ongoing management of these cases.

Some of the various strategies that clinicians have tried in practice include increasing the dose of therapy,[21,22] or changing the dosing regimen from preseasonal to continuous AIT (for seasonal allergens).[23] Clinicians have also switched products—in order to utilize different adjuvants, [24,25] switched from SLIT to SCIT and vice versa,[26] or considered the use of both SLIT and SCIT concurrently.[27]

In case 3, subsequent options being considered are to persist with a second year of *Pollinex® Quattro* or aim for higher dose treatment of *Alutard SQ®* (300 000 SQ-U maintenance dose) as there had been partial response.

Decisions regarding switching therapies should involve detailed assessment and consideration of patient preferences. The clinical assessment should include symptoms, medication use, and side effects. Objective assessment such as the Rhinitis Quality of Life Questionnaire may offer particular value in serial assessment.[17,28,29] Patient adherence is important to assess and monitor, particularly with SLIT, as this can underlie therapeutic failure. In our 4 cases, the patient adherence was excellent. While safety is always of paramount importance, the search for an alternative may lead to a product which does not offer similar published efficacy (eg, case 1).[30,31]

Selection of Allergen

The selection of allergen can contribute to AIT success. Asero et al. reported that choice of ragweed allergen had a major influence on AIT response in an area of Italy to the north of Milan.[32] This area is predominantly characterized by short ragweed. Giant and short ragweed species show significant cross-reactivity, and usually one species is satisfactory for skin testing and AIT. However in the above geographical location, about half of the patients showed a lack of response to giant ragweed AIT, but excellent response when changed to short ragweed AIT.

The issue of patients with evidence of allergen-specific IgE to multiple allergens has been alluded to within the various guidelines.[16,17,20] The distinction between polysensitized and polyallergic is not always clearcut based on history alone, and the correct selection of allergens is critical to AIT response in this group.

Component Resolved Diagnosis

The British Society for Allergy and Clinical Immunology (BSACI) guidelines refer to the potential of component resolved diagnosis in AIT.[18] Many allergens are mixtures of various proteins ("components") to which individuals are variably sensitized. These individual components have variable clinical relevance, in that they are associated with variable risk of developing clinical symptoms of AR. Selection of patients according to "*component resolved diagnosis*" may facilitate identification of

Table 1. Possible Reasons for Inadequate Clinical Response to AIT.

Reason	Example
Incorrect allergen selection	Incorrect species of grass for individual patient
Multiple allergens	Inappropriate selection in patient with polysensitivities and/or polyallergies
Inappropriate composition of allergen preparation	Insufficient amount of a particular allergen or allergen component in a mixed allergen preparation
Inappropriate dosing	Dosing is often derived from clinical trial data, rather than individually tailored to the patient
Insufficient duration of treatment	Systematic reviews now suggest a minimum of 3 years, but this may not be sufficient in some patients
Suboptimal patient adherence	Can be problematic and not always apparent, particularly with SLIT

Abbreviations: AIT, allergen immunotherapy; SLIT, sublingual immunotherapy.

Table 2. Comparison of British, European, and American Guidelines for the Patient Selection Process for AIT Administration and Failure of Clinical Response.[16–20]

	BSACI	EAACI	AAAAI
Patient selection	1) Accurate identification of allergic trigger: • Relevant symptoms • SPT • +/or serum sIgE • Inadequate response to optimal pharmacotherapy 2) Excluded: • Significant nonseasonal asthma • Concomitant β-blockers • Not initiated in pregnancy 3) Role of component resolved diagnosis	1) Meet indications for AIT: • Moderate-to-severe AR • Failure of response to pharmacotherapy • Relevant SPT or serum sIgE results 2) Excluded: • Uncontrolled/severe asthma • Uncontrolled autoimmunity • Active malignancy • Not initiated in pregnancy	1) Meet indications for AIT: • Relevant SPT or serum sIgE results Consider • Severity and duration of symptoms • Effect of symptoms on patient QoL • Failure of response to pharmacotherapy • Patient choice 2) Excluded: • Severe uncontrolled asthma • Not initiated in pregnancy
Therapy protocol when the correctly selected patient fails to respond	Not in guidance	Not in guidance Not all the patients benefit from AIT; need for further stratification approaches to better identify responders	Not in guidance

Abbreviations: AAAAI, American Academy of Allergy, Asthma, and Immunology; AIT, allergen immunotherapy; AR, allergic rhinitis; BSACI, British Society for Allergy and Clinical Immunology; EAACI, European Academy of Allergy and Clinical Immunology; QoL, quality of life; sIgE = allergen-specific IgE; SPT, skin prick testing.

better AIT responders. This may also lead to bespoke production of AIT products on an individual basis.[33] In all our patients, the grass components Ph1 p 1 and Ph1 p 5 were positive, indicating that a good response to AIT would be expected. Despite being "correctly" selected even at a molecular level, AIT failed to have a good clinical outcome.

Duration of Treatment

The guidelines also vary in their recommendations for duration of treatment. BSACI guidelines recommend discontinuation if no response after 2 years.[18] This was also proposed in a 2019 review from the Durham group.[8] Interestingly, the Grazax Summary of Product Characteristics in the United Kingdom advises to stop after 1 season if no improvement.[34] The European Academy of Allergy and Clinical Immunology (EAACI) guidelines propose a minimum duration of 3 years of treatment.[20] They note that there should be a reassessment if there is a lack of benefit of AIT after 1 year according to patient and physician. The German guidelines propose that if the treatment shows no signs of success after 1 to a maximum of 2 years, it should be critically reappraised; if possible by the physician who established the indication for AIT.[35] In case 2, therapeutic effect was reached only after 3 years. We acknowledge that the outcome in case 2 could not be strictly considered to be a "failure." We included this case as the BSACI, EAACI, and German guidelines suggest reviewing whether to continue with AIT if no response at 1 to 2 years.[16,20,35] Following these guidelines strictly would have deprived this patient of the therapeutic benefit which he experienced in year 3.

The American Academy of Allergy, Asthma, and Immunology (AAAAI) practice parameters suggest that a decision about continuation of *effective* immunotherapy should generally be made after an initial period of 3 to 5 years treatment.[17] The International Consensus (ICON) guidelines suggest a duration of 3 years of AIT for AR but also refer to evidence from a long-term open controlled study suggesting that a 3-year course of SLIT might not be sufficient for a long-term protection.[7,36] In this prospective 15-year study, Marogna et al. suggested a 4-year SLIT course was optimal because it induced a long-lasting clinical improvement similar to a 5-year course, but better than the 3-year course.[36] Des Roches et al. reported in a study of house dust mite SCIT that the duration of efficacy related to the duration of SCIT administration.[37] The Allergic Rhinitis and its Impact on Asthma (ARIA) care pathways refer to future development of "early" and "late" stopping guidelines, akin to those used for biologics in severe asthma.[4]

Tolerability

Reviews and guidelines (British, European, and American) also do not advise treatment paths to take when intolerable side effects are experienced, necessitating discontinuation of AIT. Initial local effects are common and transient with SLIT—in the vast majority, local reactions subside, and patients should be encouraged to continue. Temporary dosage reduction and reescalation can sometimes be effective. However in rare patients such as case 1, the symptoms can be persistent and troublesome. The ARIA guidelines suggest in the rare event of a general allergic reaction after SLIT, then risk/benefit should be reassessed and a decision made whether to continue SLIT and, if appropriate, whether an adrenaline auto-injector should be provided. In the United States, adrenaline autoinjectors are often routinely coprescribed as rescue medication for SLIT patients.[4]

In clinical practice, alternative products might be used or AIT in combination with anti-IgE monoclonal antibodies, for example, omalizumab. Known side effects are only mentioned in the guidelines as a consideration when weighing up treatment options. Although risk factors for severe side effects have been identified such as symptomatic asthma, prior SCIT-related systemic reactions, and a high degree of skin test reactivity, subsequent management options for intolerable side effects have not been addressed.[7,17] The ICON guidelines briefly mention strategies including different adjuvants or stimulating the innate immune system as strategies under development to improve the side-effect profile of AIT.[7] More positively, future developments which may improve tolerability are discussed in the wider literature[38,39] and include glutaraldehyde-modified allergoids, recombinant allergen preparations,[38] peptide immunotherapy and peptide-carrier immunotherapy,[40,41] alternative modes of delivery (intralymphatic, epicutaneous administration)[42,43] and combination or pretreatment with biological agents such as anti-IgE [omalizumab] or anti-interleukin 4.[44,45] Utilization of allergen-delivery systems such as liposomes may allow more effective sublingual administration of allergen, but lower risk of inducing local side effects, which would otherwise be dose-limiting.[46]

Relapse

The AAAAI guidelines allude to the situation of early relapse after AIT completion similar to our case 4—they note, however, that there are no specific markers to predict who will remain in clinical remission after completion of effective AIT. The duration of the maintenance phase varies in different centers between 3 and 5 years and should also be guided by individual patient assessment.[17,47] While there is evidence to suggest that a minimum of 3 years reduces relapse risk, the data between 3 and 5 years are insufficient to definitively compare relapse risk.[17,48,49] There is no guidance as to *standard* practice in such cases where there is an early relapse of AR symptoms. Ebner et al. noted a relapse rate of 3% in the first year after completion of 3 to 4 years of grass/rye SCIT, rising to 30% by year 3. This group also noted that in these relapsing patients, administration of preseasonal SCIT could subsequently be effective.[50]

Case 4 had a relapse of her hay fever symptoms in the season immediately following discontinuation. After clinical assessment, and discussion with the patient, the plan is to try *Grazax®* SLIT in the first instance.

This review must alert allergists and immunologists to the fact that therapeutic failure exists, that it is poorly characterized, and that we have no good data for how often it is occurring. In our own cohort, our therapeutic failure rate was 4/660 (0.6%). There is published literature available which can assist in the management of such cases,[21–27] but the gap in the guidelines should evoke interest to generate AIT failure rate data in order to develop *standardized* protocol(s) when therapeutic failure arises. At the present time, clinicians are developing *individualized* protocols based on opinion and observational work when a correctly selected patient fails to achieve a clinical response to AIT. In addition, there are also no protocols on the optimal treatment strategy if AIT has to be discontinued due to severe side effects.

Conclusions and Future Directions

There remain major gaps in the literature and in guidelines. Future studies are required in order to (1) optimize AIT efficacy by avoiding treatment failure, and improving management of side effects which can lead to treatment discontinuation; (2) help better predict which patients will respond or fail on AIT—the literature simply states that AIT is effective in "the majority" of patients[51]; (3) establish criteria for treatment failure, which are not well defined; (4) identify national/international data for patients who do not respond to SLIT/SCIT—we only have statistics for our own cohort; (5) review the ongoing debate about the duration of AIT treatment; (6) determine optimal duration of AIT should be tried before deciding that treatment failure has occurred; (7) delineate clinical and/or biochemical end points for when clinicians need to recognize AIT failure and stop exploring alternative treatment options.[4]

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Ethical Approval

We confirm that Ethical Committee approval was not necessary, and this is acknowledged within the text of the submitted manuscript.

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Statement of Human and Animal Rights

We confirm that guidelines on animal rights and treatment have been met and any details of approval obtained are indicated within the text of the submitted manuscript – this statement is not relevant to our work.

Statement of Informed Consent

We confirm that guidelines on patient consent have been met and any details of informed consent obtained are indicated within the text of the submitted manuscript.

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