

## REVIEW ARTICLE

# Recent developments and highlights in rhinitis and allergen immunotherapy

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Email: somasundram\_subramaniam@nuhs.edu.sg**Abstract**

This review paper aims to provide an overview of recent developments in the field of allergic and non-allergic rhinitis, as well as allergen immunotherapy. Recent advances in phenotyping and endotyping various forms of rhinitis have brought us one step closer towards tailoring treatment more appropriately for a given patient. Updates on local allergic rhinitis are also covered. Allergen immunotherapy (AIT) is an area of significant interest, with multiple original papers and recent position papers and guidelines published. Evidence related to the application of AIT in seasonal and perennial allergic rhinitis (AR), local allergic rhinitis and novel and expanded applications is discussed in the publication.

**KEYWORDS**

allergen immunotherapy, allergic rhinitis, local allergic rhinitis, non-allergic rhinitis

## 1 | INTRODUCTION

This review focuses on recent developments in the diagnosis, treatment and consequences of allergic and non-allergic rhinitis, and highlights the most recent updates in the use of allergen immunotherapy in the treatment of allergic rhinitis. Several recent key findings in the (differential) diagnosis of rhinitis have changed our way of thinking about the disease. The PRACTALL report describes in depth the phenotypes and endotypes of rhinitis, where interesting new concepts have seen the light.<sup>1</sup>

## 2 | PHENOTYPING OF RHINITIS

Phenotyping of rhinitis has important consequences in the treatment of the disease.<sup>2</sup> Usually, it is possible with a careful history combined with skin prick testing to at least determine whether there is an underlying sensitization explaining the symptomatology. Contrary to the lower airways,<sup>3</sup> it was long thought that hyperreactivity was

mainly a feature of non-allergic rhinitis. However, Segboer et al<sup>2,4</sup> showed that patients with allergic rhinitis (AR) and non-allergic rhinitis (NAR) have the same amount of hyperreactivity. Also, again contrary to the lower airways, hyperreactivity is widely neglected during history taking, underdiagnosed in the majority of rhinitis patients and not considered as a target for treatment or a relevant outcome parameter in clinical trials.<sup>5</sup> An important reason for this neglect might be that hyperreactivity can only be reliably measured with cold dry air provocation (CDA). Contrary to pulmonary function tests, nasal function tests like CDA are not performed on a daily base. However, in clinical practice, nasal hyperreactivity can be diagnosed with a simple clinical history with specific questions directed at the detection of nasal symptoms being induced by exposure to environmental triggers and/or stress factors. Care should be taken to distinguish these nasal complaints from the normal nasal cycle.<sup>6</sup> When in doubt, a nasal function test to evaluate fluctuations in nasal obstruction that can be done easily and can even be done at home is Peak Nasal Inspiratory Flow (PNIF).<sup>7-10</sup>

**Abbreviations:** AA, allergic asthma; AIT, allergen immunotherapy; AR, allergic rhinitis; CDA, cold dry air provocation; DB-RCT, double-blinded randomized controlled trial; EAACI, European Academy of allergy and clinical immunology; HAART, highly active antiretroviral therapy; HDM, house dust mite; MP29-02, fluticasone propionate and azelastine hydrochloride combination; NAPT, nasal allergen provocation test; NARES, non-allergic rhinitis with eosinophilic syndrome; NAR, non-allergic rhinitis; NSAID, non-steroidal anti-inflammatory drugs; PNIF, peak nasal inspiratory flow; SAR, seasonal allergic rhinitis; sIgE/tIgE, specific Immunoglobulin E-to-total immunoglobulin E ratio; SLIT/SCIT, sublingual/subcutaneous allergen immunotherapy; Th2, T helper 2 cells; TRPV1-SP, transient receptor potential vanilloid 1—substance P.

Reitsma and Subramaniam contributed equally to this work.

The Position paper of the European Academy of Allergy and Clinical Immunology on Non-allergic rhinitis emphasizes the importance of careful history and examination of patients with rhinitis.<sup>2</sup> Most of the subgroups of NAR can easily be distinguished in this way. The importance of a careful history has been emphasized by the recent publication of papers on the prevalence of NAR in swimmers<sup>11-13</sup> and in patients with sleep disorders.<sup>14</sup> Also, occupational provocation is often forgotten.<sup>15</sup> Moreover, it is important to realize that NAR with significant hyperreactivity can be the first symptom of NSAID-exacerbated disease. Because NSAID usually leads to severe airway disease with chronic rhinosinusitis and asthma,<sup>16,17</sup> it is important to recognize it early in the disease process. Evidently, the lower airways should be included in a careful history as rhinitis is often accompanied by pulmonary problems, as described by the unified airway concept.<sup>18-21</sup>

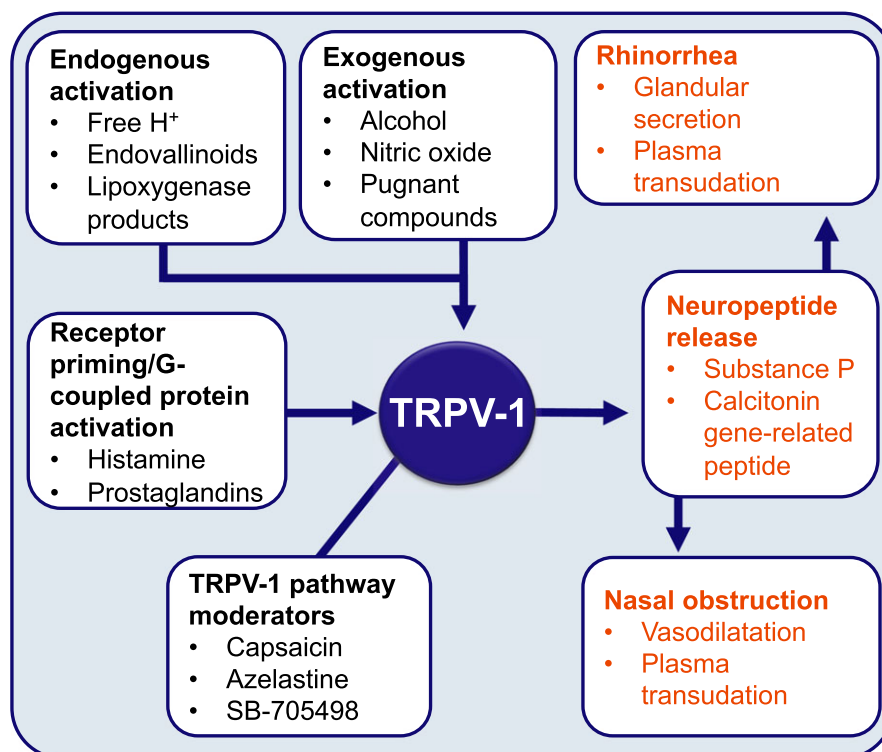
### 3 | TREATMENT OF NASAL HYPERREACTIVITY AND NAR1

Until recently, most studies on the treatment of nasal hyperreactivity were done in NAR where it has been shown that treatment with capsaicin is able to reduce nasal hyperreactivity by ablating the TRPV1-SP nociceptive signalling pathway in the nasal mucosa (Figure 1).<sup>22</sup> Also, intranasal SB-705498, a selective TRPV1 antagonist, is able to reduce capsaicin-induced nasal hyperreactivity in patients with NAR.<sup>23</sup> Capsaicin is one of the very few treatments, if not the only, that is effective in idiopathic rhinitis (IR),<sup>24</sup> one of the most common forms of NAR.<sup>2</sup> Very recently, it was reported

that capsaicin nasal spray is effective in a broader group of NAR patients than IR patients alone, that subjective nasal hyperreactivity is a good predictor of positive outcome, but that the time interval for seeking a second treatment is likely to be shorter in this broader NAR group than in IR.<sup>25</sup> Although there is one small study showing that capsaicin is not effective in allergic rhinitis patients,<sup>26</sup> it might be worthwhile to perform a larger study in all patients with significant hyperreactivity irrespective of sensitization. Another interesting potential treatment in NAR could be the combination of a nasal corticosteroid with azelastine (MP29-02).<sup>27,28</sup> MP29-02 has been shown to specifically reduce nasal hyperreactivity and nasal mediators in patients with house dust mite-allergic rhinitis.<sup>29</sup> Azelastine, similar to capsaicin, reduces the membranous expression of the TRPV1 receptor and exhibits direct activity on TRPV1 ion channels that may represent a novel mechanistic pathway explaining its clinical efficacy in NAR.<sup>30</sup>

For now, it is clear that NAR represents a heterogeneous group of mucosal pathology of variable severity and with a heterogeneous underlying aetiology. NAR has a significant impact on quality of life similar or even larger than AR<sup>31,32</sup> and warrants more attention in our daily clinical work. The heterogeneity of the disease warrants a personalized management approach like in other upper airway diseases.<sup>33-35</sup> Also, comparable to AR<sup>36-39</sup> and maybe even more because of the lack of treatment options, it can be expected that NAR has a significant impact on work productivity and has a significant health impact, although data are lacking at the moment. More and better studies on prevalence, including phenotyping and endotyping, on the efficacy of different (endotype-driven) treatment options in NAR patients and the role of hyperreactivity are urgently needed.<sup>2</sup>

**FIGURE 1** Schematic representation of the TRPV-1 pathway in non-allergic rhinitis. The TRPV-1 receptor can be activated by both endogenous and exogenous pathways. When primed, by activation of various G-coupled proteins, it will be more susceptible to activation. TRPV-1 activation will lead to antidromic release of substance P and calcitonin gene-related peptide, in turn provoking vasodilatation, plasma transudation and increased glandular secretion in the nose. As a result, patients complain of rhinorrhoea and nasal congestion. TRPV-1: Transient receptor potential vanilloid receptor 1



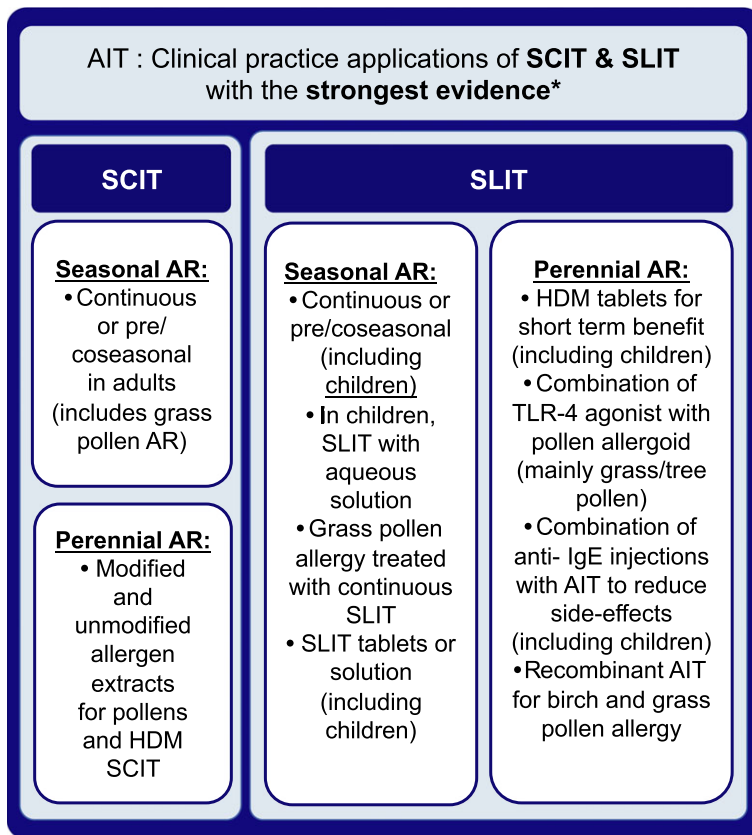


**FIGURE 2** Allergen immunotherapy (AIT): Clinical practice applications for SCIT and SLIT with the strongest evidence. This figure summarizes and extracts the highest level evidence (level 1 based on systematic review, meta-analysis and randomized controlled trial data) based upon the April 2018 EAACI guidelines on allergen immunotherapy: allergic rhinoconjunctivitis, with regard to clinical applications of AIT

#### 4 | LOCAL ALLERGIC RHINITIS

In southern Europe, in recent years a lot of emphasis has been placed on the existence of local allergic rhinitis (LAR),<sup>40-43</sup> although the high prevalence reported in Spain has not yet been confirmed elsewhere.<sup>2,44,45</sup> LAR can be suspected by a history of allergen-induced symptoms without signs of systemic sensitization. The diagnosis of LAR needs to be confirmed by the detection of nasal specific IgE, a positive nasal allergen provocation test (NAPT)<sup>46</sup> or both.<sup>47</sup> It can be debated whether LAR should be defined as a subgroup of NAR or a subgroup of AR. Because the underlying pathophysiology is very similar to AR and also treatment response is very similar to AR,<sup>40,42</sup> it might be more logical to define LAR as a special form of AR. Although nasal corticosteroids do not seem to be very effective in NAR in general, subgroups like NAR with eosinophilia syndrome (NARES) and LAR might be susceptible to this treatment. At the moment studies proving this are, to our knowledge, not available.

#### 5 | ALLERGIC RHINITIS AND ALLERGEN IMMUNOTHERAPY

In allergic rhinitis, treatment will be significantly influenced by studies in real-life environment,<sup>32,38,43,48-54</sup> evaluating the effectiveness of on-demand treatment.<sup>55,56</sup> In order to collect data from patients in a more efficient and timely manner, mobile technology in the

form of a phone app (the MASK-rhinitis Allergy Diary) allows monitoring of allergic rhinitis symptoms and disease control data.<sup>57</sup> Other such apps in the near future will facilitate more accurate collection of patient data in an increasingly seamless manner than is possible today.

Allergen immunotherapy (AIT) has been shown to be highly efficacious in the treatment of immunoglobulin E (IgE)-mediated allergic disease for long-term symptom control in allergic rhinitis and asthma. It also prevents progression of allergic rhinitis to asthma in children and reduces the sensitization of at-risk infants to house dust mite allergy.<sup>54,58-63</sup>

Despite its widely reported safety, efficacy and its cost-effectiveness,<sup>64,65</sup> AIT remains under-utilized due to a variety of reasons: lack of agreement between documented efficacy, insufficient data on its cost-effectiveness, lack of awareness on AIT and lack of uniformity in the regimens and/or products for use. Action has been taken to address several of these challenges, amongst these, the EAACI AIT guidelines (Figures 2 & 3) based upon systematic reviews and meta-analyses.<sup>66-69</sup> However, what remains a challenge is the heterogeneity and gaps in the data available, making it difficult to make evidence-based clinical recommendations. Gaps in the evidence that current and future research needs to clarify include the long-term benefit of AIT, the paediatric population, its use in polysensitized patients, the value of AIT for primary prevention, identifying biomarkers to select responders and monitor efficacy objectively, and cost-effectiveness analyses.<sup>70-73</sup>

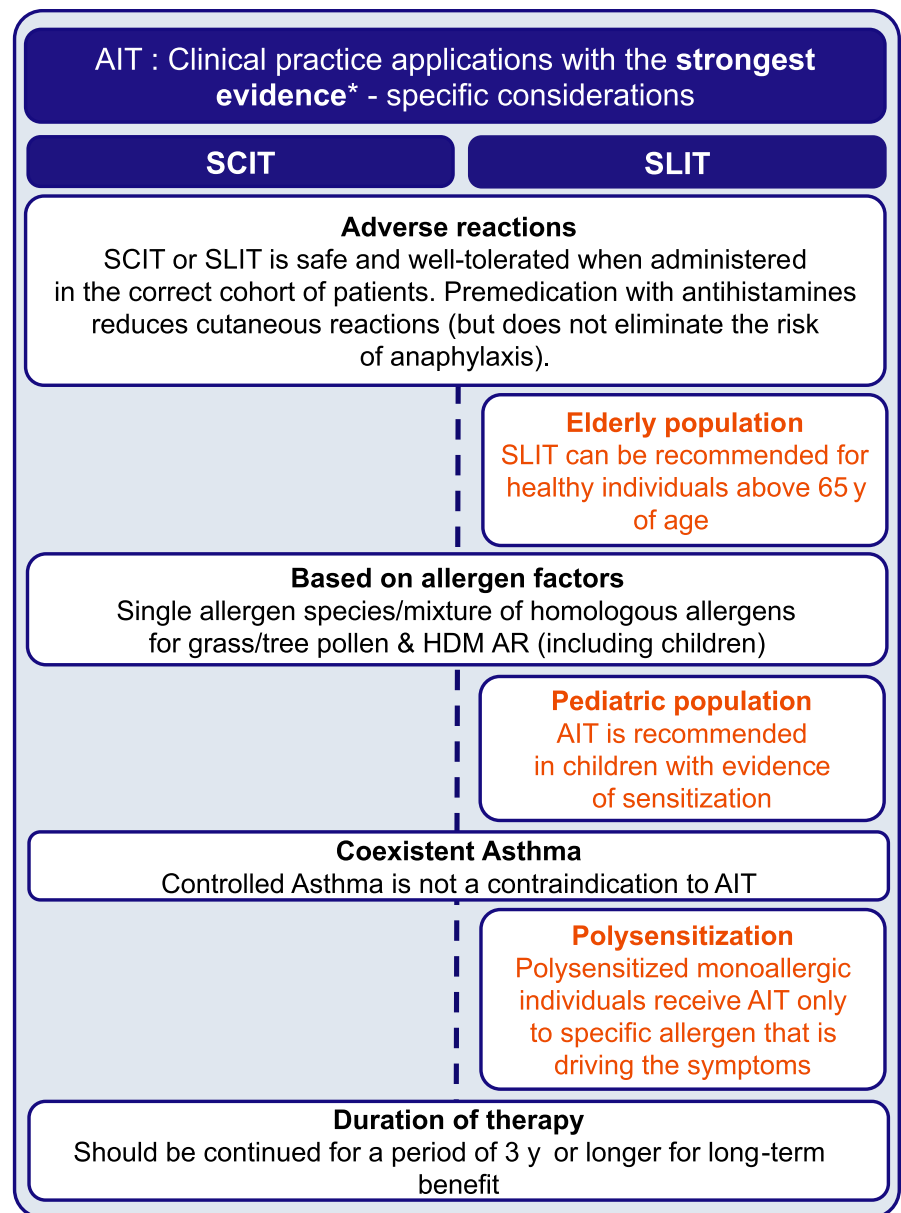


**FIGURE 3** Specific considerations related to allergen immunotherapy (AIT) in clinical practice. Based upon the same evidence as Figure 2, Figure 3 divides the available level 1 evidence on SCIT and SLIT into two categories. Some evidence was based upon papers that utilized SCIT only (left half of diagram) or SLIT only (right half of diagram), and others included a combination of both (across midline into both halves)

*\*All listed are Grade A (Level 1 evidence) recommendations based on the EAACI guidelines on allergen immunotherapy : Allergic Rhinoconjunctivitis Apr 2018*

## 6 | RECENT DEFINITIONS, POSITION PAPERS ON AIT AND REVIEW OF GUIDELINES

Recently released EAACI definition on pollen season was confirmed to correlate with symptom loads for grass and birch pollen-induced AR.<sup>74</sup> In addition, since there is a lack of data in defining pollen exposure intensity or time period, a recent EAACI position paper defined pollen exposure times for different pollen types to be used in AIT trials.<sup>75</sup>

Several position papers have recently been published, pertaining to standardizing nasal allergen challenges,<sup>46</sup> identifying the role of biomarkers<sup>76</sup> and challenges in the implementation of the EAACI

guidelines on allergen exposure chambers.<sup>77,78</sup> With regard to biomarkers, there are currently no validated or widely accepted candidates that are predictive of clinical response to AIT. However, several measurements have emerged as forerunners in this field: allergen specific IgG4 as a biomarker for compliance, as well as sIgE/tIgE and IgE-FAB. Allergen exposure chambers show promise in future trials to determine safety and efficacy of therapeutics. The EAACI taskforce set out to standardize multiple parameters amongst chamber operators in order to allow better future comparative studies.

In a recent review of the quality of AIT guidelines (both national and international) using AGREE-II principles, the highest score went to German-Austrian-Swiss guidelines.<sup>79</sup>

## 7 | UPDATES IN SEASONAL ALLERGY AND AIT (INCLUDING RELATED FOOD ALLERGY)

The use of short-course (either 3 or 6 weeks) subcutaneous grass allergen peptide AIT was shown in studies to be safe and effective in significantly reducing seasonal symptoms. It was also shown to induce blocking antibody formation as early as 4 weeks following treatment initiation.<sup>80-83</sup>

In birch-related food allergy, there were significant immunogenic effects in patients treated with AIT to recombinant Bet v 1, with some symptomatic (but not statistically significant) improvement.<sup>84</sup> Also, recombinant Mal d1 was shown to be a safe option in assessing clinical reactions in birch-related apple allergic individuals through dose-defined sublingual challenge testing.<sup>85</sup>

With regard to non-AIT treatment options for seasonal allergic rhinitis (SAR), a recent DB-RCT phase II study on the effects of a novel prostaglandin D2 receptor-1 antagonist (DP1), ONO 4053 on patients with SAR, showed that in comparison with leukotriene receptor antagonist (Pranlukast) and placebo, ONO 4053 has a higher efficacy compared to the other 2 groups, with a similar safety profile.<sup>86</sup>

## 8 | UPDATES IN HOUSE DUST MITE (HDM) AIT

A recent large-scale double-blinded Japanese trial involving 1 year of sublingual HDM AIT showed effectiveness in symptom control, without major safety concerns.<sup>87</sup> To address the issue of the optimal safe and effective allergoid dose, a randomized 5-arm dose finding study found that concentrations between 20 000 and 50 000 AUeq/mL exhibited the best risk-benefit ratio.<sup>88</sup> When comparing crude allergen extract vs purified or recombinant allergens, both suppress airway hyperresponsiveness and eosinophilic inflammation, while the purified form induces greater suppression of Th2 cells and HDM-induced airway epithelium.<sup>89</sup> Another DB-RCT study on HDM-associated allergic rhinitis identified a dose-dependent effect of SLIT, when conducted in an environmental exposure chamber.<sup>90</sup>

Taking into account differing patterns of IgE sensitization in Dermatophagoides-allergic patients from different geographical areas, a recent study found that mite-specific AIT utilizing a mixture of *D. pteronyssinus* and *D. Farinae* extracts from the faeces and bodies makes it appropriate to treat adults and children from diverse geographical locations.<sup>91</sup>

On a related area of the presence of allergic asthma (AA) co-existing with allergic rhinitis, specifically with regard to HDM allergy, current guidelines lack specific recommendation for the treatment of AA. In this scenario, recent studies have strengthened the evidence base for this, but more work in this area will be required to allow future guidelines to give better recommendations.<sup>92</sup>

## 9 | AIT IN LOCAL ALLERGIC RHINITIS (LAR)

As mentioned above, local allergic rhinitis has been defined as a subset of patients that demonstrate local nasal responses with typical allergic rhinitis symptoms in the absence of atopy and systemic responses. Correct identification of LAR is important (to differentiate it from non-allergic rhinitis—NAR) as these patients respond to allergen avoidance, as well as AIT.<sup>41</sup> Two DBPCT studies from the Malaga group, one for 1 year in grass pollen and one for 2 years in HDM, have shown clinical effectiveness for AIT in the study period.<sup>40,42,93</sup>

## 10 | EXTENDED AND NOVEL APPLICATIONS OF AIT

In human cohorts, where HIV infection was previously a relative contraindication for AIT, a recent study showed that the use of sublingual AIT in in-vitro immunologically controlled HAART-treated HIV-positive patients (who were grass pollen-allergic) was efficacious, safe and well-tolerated.<sup>94</sup>

As for the use of adjuvant agents in AIT, a recent trial where bacterial flagellin (a Toll-like receptor 5 agonist used as an adjuvant for immunomodulation) was administered via intranasal, sublingual and intralymphatic routes, the latter route showed more effective suppression of allergic inflammation.<sup>95</sup>

In the application of AIT in animals, similar immunological mechanisms to humans have been shown (including production of blocking IgG antibodies). The strongest evidence for AIT exists for dogs (where subcutaneous AIT is used in atopic dermatitis). Promising pilot studies involving horses have demonstrated the benefit of AIT in insect hypersensitivity using recombinant antigens of biting midges.<sup>96</sup>

## 11 | CONCLUSIONS

There has been a significant amount of progress made in expanding our understanding of allergic and non-allergic rhinitis, as well as allergen immunotherapy in recent years. This paper summarizes the salient points from recent studies in each of these areas to give the reader a broad and succinct overview of this progressively evolving field.

### CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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