

Preventing Progression of Allergic Rhinitis to Asthma

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Abstract The prevalence of allergic rhinitis (AR) is on the increase and this condition is frequently associated with asthma, thus leading to the concept that these two conditions are different aspects of the same disease. There is now accumulating evidence that AR often precedes the onset of asthmatic symptoms. This notion has important implications, not only for the diagnosis and management of these common allergic conditions but also for the potential progression of disease. Very little is known about the risk factors responsible for the progression of AR to asthma; current treatment options can control symptoms but do not prevent or cure the disease. However, there are recent data supporting the notion that it is possible to prevent new asthma cases by modifying the immune response and clinical outcome with allergen immunotherapy. This review article evaluates the impact of AR on the development of asthma, examines putative predictors for the progression of AR to asthma, and reviews recent, promising literature suggesting that early treatment of allergic individuals with immunotherapy may aid in asthma prevention.

Keywords Atopic march · Allergic rhinitis · Asthma · Progression · Specific immunotherapy · Predictors · Prevention

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Introduction

Rhino-sinusal disease is a common co-morbidity of asthma. Allergic airways disease affects the mucosal lining and spans from the nose to lungs with a range of symptoms depending on the site affected and its severity [1, 2]. Additionally, both organ systems are equipped with a common lymphoid network and can respond to airborne allergens by activating similar effector cells. These close anatomical, functional, pathogenic, immunological and clinical links between the upper and lower respiratory tract have been extensively investigated and suggest that allergic airways disease represent a disease continuum rather than discrete parallel entities occurring simultaneously [1–4]. Several prospective studies of patients with severe asthma have shown that those who also had upper airway involvement reported more emergency room visits and a more severe disease [5–7]. As a result of this, the terms united airways disease, allergic rhinobronchitis and/or allergic rhinitis and asthma syndrome (CARAS) have been coined by various researchers [2, 8, 9].

Further justification for the combined allergic airway paradigm derives from the evidence that nasal allergen challenge induces bronchial inflammation/hyperresponsiveness [10], and that segmental bronchial provocation can induce nasal inflammation in subjects with allergic rhinitis (AR) without asthma [11]. It has also been reported that in 605 non-asthma subjects with AR, 8.4 % had an abnormal FEV1, 24.7 % had impaired small airways measurement as measured by FEF25–75 and 66.1 % had bronchodilator reversibility [12•]. These studies point to a strong association between allergic nasal disease and atopic asthma with a prevalence that may be as high as 80 % [13, 14]. In a recent study of approximately 200 AR subjects, the authors found that FeNO was a potential predictive marker for BHR in AR patients and underlined the close link between upper and lower airways. This indicates that increased FeNO in subjects with rhinitis could be an indicator of the risk of developing asthma [15].

The notion that upper and lower respiratory airways represent a disease continuum lends support to the ‘allergic/atopic march’ hypothesis (i.e. the sequential development of allergic manifestations of atopic conditions in early childhood) [13, 16]. A number of prospective studies demonstrate that there is evidence for the progression of atopic dermatitis (AD) and/or AR into allergic asthma [13, 17]. Here, we will discuss the impact of rhinitis on the development of asthma, examine the putative predictors for the progression of rhinitis to asthma and review the literature in relation to the use of allergen immunotherapy (IT) for the prevention of asthma in atopic individuals.

Progression from Rhinitis to Asthma Across the Allergic Disease Continuum

The prevalence of AR is on the rise, and this condition frequently overlaps with asthma [18]. It has been reported that AR currently affects up to 40 % of the worldwide population and that as many as 40 % of rhinitic patients had asthma and that up to 80 % of asthmatics had nasal allergic symptoms [19, 20].

Similarly, in a proportion of AR patients, bronchial provocation challenges resulted in significant bronchial hyperresponsiveness (BHR) despite the absence of asthma symptoms [21, 22], suggesting a subclinical background inflammation in the lower airways [23–25]. The presence of BHR in non-asthmatic AR patients has been shown to be a risk for progression to asthma [26–28].

Several studies suggest that rhinitis may predict progression to asthma both in children and adults [29–38]. This may be due to the fact that these entities are manifestations of a progressive condition, or a reflection of distinct disease process afflicting a susceptible population. The former is probably more likely as there is a wealth of evidence suggesting that the upper airway symptomatology experienced by asthmatics is unique: there is a similar inflammatory pathophysiology and severity in the upper and lower airways.

In the Tasmanian Asthma longitudinal study, it was reported that childhood AR was associated with a 2- to 7-fold increased risk of asthma in later life; and the presence of childhood AR increased the possibility of childhood asthma persisting into later life compared to remission by middle age [33]. Recently, a further assessment of the same population has confirmed the lack of association between childhood eczema or rhinitis and non-atopic adult asthma; however, the combination of eczema and rhinitis predicted new-onset atopic asthma by middle age (odds ratio, OR 6.3) and the persistence of childhood asthma to adulthood atopic asthma (OR 11.7) [39••]. They also found that the presence of childhood eczema increased the risk of new-onset asthma (OR 4.1) and rhinitis alone predicted the persistence of childhood asthma to

topic asthma (OR 2.7). Similar results were confirmed by a multi-national cross-sectional study by Leynaert and colleagues, indicating that the odds ratio of asthma (6.63) and BHR (3.02) was markedly elevated in patients with rhinitis compared to those without, implying that rhinitis increases the risk of asthma [37]. Of interest, the risk of developing asthma from rhino-sinusal disease, has been reported to be about 3–4 times more elevated compared to those without the condition and this was shown to be irrespective of allergic status [30, 35, 36].

Data from epidemiological studies have limitations and hence may be susceptible to interpretation bias. This is because these epidemiological studies rely on written questionnaires for the diagnoses of AR and asthma. Moreover, there is the possibility that some of the medications for the treatment of AR may mask developing symptoms of asthma and therefore diminish the accuracy of the diagnosis. However, epidemiological findings of the progression of rhinitis to asthma have been substantiated by prospective clinical studies [29, 31, 38]. In the prospective multi-centre, open-labelled randomised paediatric European study of 205 children with grass- and/or birch-induced rhinoconjunctivitis receiving specific immunotherapy (SIT) or not, it was reported that children not treated with SIT had an OR of 2.52 more of asthma symptoms and hence developing asthma compared to those who received SIT [29]. In a later report of a further 2-year follow-up of the same cohort of children similar findings were noted [31]. Likewise, in a retrospective Italian study of over 300 atopic subjects, a prior diagnosis of AR markedly and independently was predictive of developing asthma at 10-year follow-up; 46 % of subjects with rhinitis developed asthma symptoms at follow-up versus 7.7 % in those that did not, with an OR of 7.8 [38]. Of note, topical corticosteroid usage in the AR subjects progressing to develop asthma symptoms (52.3 %) compared to those who did not (47.5 %) were similar.

Predictors for the Progression from Rhinitis to Asthma

Repeated exposure to inhaled antigens with potent allergenic properties may eventually dictate the advancement of the ‘allergic march’ towards asthma in patients with an allergic predisposition [40]. The most common allergen implicated in the development of asthma is the house dust mite [41, 42]. Unexpectedly, in a retrospective Italian study, house dust mite sensitization was not markedly predictive of asthma onset with an O.R. of 1.33 (0.85–2.08), but sensitization to *Parietaria judaica* was with an OR of 4.26 (2.78–6.54) [38]. Although these discrepancies are unexplained, they may be a reflection of specific inhaled allergen characteristics in the locations where the individuals live or where the studies were conducted. It is well known that the presence of pets within

the household and a positive atopic family history is predictive of the development of asthma. This was confirmed in a retrospective study, but their population attributable risk was much lower than expected [38]. Of interest, the length of rhinitis duration was not predictive of the development of asthma. Gender and the presence of BHR in rhinitic patients has been associated with the onset of asthma [26–28, 43]. The former may be due to hormonal modifications, especially the sex-dependent reduction in asthma prevalence at puberty [43]. Being female was highly predictive for the development of asthma in one study with an OR of 2.83 (1.79–4.49) [38], but most studies in the literature do not address this important factor for the progression from rhinitis to asthma.

Exposure to cigarette smoke is another important determinant of the development of asthma. It has been reported that there is a strong association between the risk of childhood asthma and wheezing with maternal and household smoking [44–46]. The role of smoking on the development of asthma was investigated in 325 non-asthmatic patients with AR. An association between smoking and the development of asthma was observed (OR 2.98) as well as a dose–response effect of smoking exposure [47]. The latter, which was assessed as pack-years, was demonstrated by a progressive increased risk of incident asthma compared to those who had never smoked by using multivariate analyses: the ORs for 1–10 pack-years, 11–20 pack-years and more than 20 pack-years were 2.14, 3.81 and 5.87, respectively. This emphasizes the idea that the quantity of cigarette smoke exposure is pivotal in dictating the evolution of diverse disease phenotypes.

In theory, environmental exposure to air pollutants may also determine progression from rhinitis to asthma in some individuals. Although it is widely accepted that exposure to ambient concentrations of air pollutants can cause short-term exacerbations in subjects with asthma and rhinitis, very little is known about their role in the initiation and progression of these allergic conditions [48].

There is great uncertainty as to why a reasonable proportion of atopic and rhinitic patients develop asthma. It is known that there are inflammatory changes in the lower airways of patients with AR without asthma [23–25], which may eventually result in the progression to asthma. It is possible that persistent exposure of the airway to inhaled allergens in association with cigarette smoke may have an additive or synergistic effect on the progression of the inflammatory processes. Cigarette smoke is a complex mixture consisting of solid particles and gases. In vivo animal and human studies show that polyaromatic hydrocarbons in the particulate phase of tobacco smoke induce TH2 immune responses and promote allergic inflammation [49]. This includes the development of allergen-specific IgE antibodies and IgE-mediated allergic conditions such as AR and asthma in sensitized individuals [50]. Thus, patients with AR who smoke may be more likely to progress to asthma. Furthermore, BHR is a well recognised

phenomenon of asthma patients with concomitant rhinitis [26–28] and is also strongly associated with smoking [51]. Hence, this may explain the higher incidence of new onset asthma in rhinitic patients who smoke.

Preventing the Progression from Rhinitis to Asthma

Besides environmental control measures and allergen avoidance, the management of AR consists of pharmacological management and SIT.

Pharmacological management focuses on treating and/or controlling specific symptoms of AR, whereas SIT targets the underlying aetiology with the effects/benefits persisting following completion of therapy, improving symptoms and reducing the need for symptomatic therapy [52].

In the following sections, we will discuss the postulated mechanism(s) of action of SIT and its role with specific reference to prevention of disease progression from AR to asthma. A summary of the published studies investigating whether early treatment of allergic individuals with SIT may prevent progression from AR to asthma is illustrated in Table 1.

Specific Immunotherapy (SIT) – Mechanism of Action

The mechanism of action of SIT is not fully understood. It is, however, based on the principle that repeated allergen administration in allergic individuals results in immune tolerance by attenuating the sensitivity to the offending allergen. It has been proposed that several modifications of the cellular and humoral immune response occur during the course of SIT administration [56–58, 59••] (Fig. 1). An initial early step in SIT may be the H2-dependent suppression of FcεR1-bearing effector cells [60•]. Following this initial step, a long-lasting desensitization is initiated by functional regulatory T (TReg) cells that will shift the TH1/TH2 cells balance in favour of TH1 milieu [56–58, 59••]. Increases in interleukin (IL)-10 from monocytes, macrophages, and B and T cells, together with elevation in transforming growth factor beta (TGFβ) as a result of SIT exposure are postulated to contribute the TReg cell function and immunoglobulin class-switching to IgG1, IgG4 and IgA. These immunoglobulins compete with IgE for allergen binding, thereby decreasing the allergen capture and presentation facilitated by IgE in complex with the high-affinity receptor (FcεR1) of low-affinity for IgE (FcεR2, CD23). In particular, IgG4 is considered a blocking antibody, inhibiting allergen-induced and IgE-mediated release of inflammatory mediators from basophils and mast cells acting both as a kidnapper of allergens and through binding to FcγRIIA and FcγRIIB receptors expressed on basophils and mast cells [61]. Additionally, IL-10 and TReg cells appear to further elevate the activation threshold level of basophils and mast cells. As a final

Table 1 Studies showing prevention of new asthma cases by allergen immunotherapy

Study	Age range (years)	Follow-up (years)	Number of patient in each group	Immunotherapy (% of patients with new-onset asthma)	Control (% of patients with new-onset asthma)	P value
Moller et al. [29]	6–15 (mean 10.7)	3	SCIT: 97 CTRL: 94	24	44	<0.05
Polosa et al. [38]	18–40	9–10	SCIT: 202 CTRL: 130	42	53	<0.05
Niggemann et al. [31]	6–15	5	SCIT: 95 CTRL: 88	20	43	<0.01
Jacobsen et al. [53]	6–14	10	SCIT: 64 CTRL: 53	25	45	<0.01
Polosa et al. [54]	20–54 (mean 33.1)	3	SCIT: 15 PLA: 15	14	47	0.056
Novembre et al. [30]	4–16 (mean 8.4)	3	SLIT: 54 CTRL: 59	18	41	<0.05
Marogna et al. [32]	5–17 (mean 10.4)	3	SLIT: 130 CTRL: 66	2	29	<0.001
Milani et al. [55]	(mean 22.5)	2	SLIT: 154 CTRL: 151	9	30	<0.01

point, IL-10 is a powerful suppressant of IL-5 production by T cells and this may consequently inhibit eosinophils activation and survival in the tissue.

Therefore, SIT—unlike symptomatic therapies—has the potential to modulate underlying allergic mechanisms and may hold a place in attenuating or halting the progression of

AR to asthma and new sensitizations. In susceptible individuals, SIT may intercept immune processes mediating asthma progression rather than reversing the immune response once the disease is established [62, 63]. The evidence for this hypothesis is now available and is discussed below.

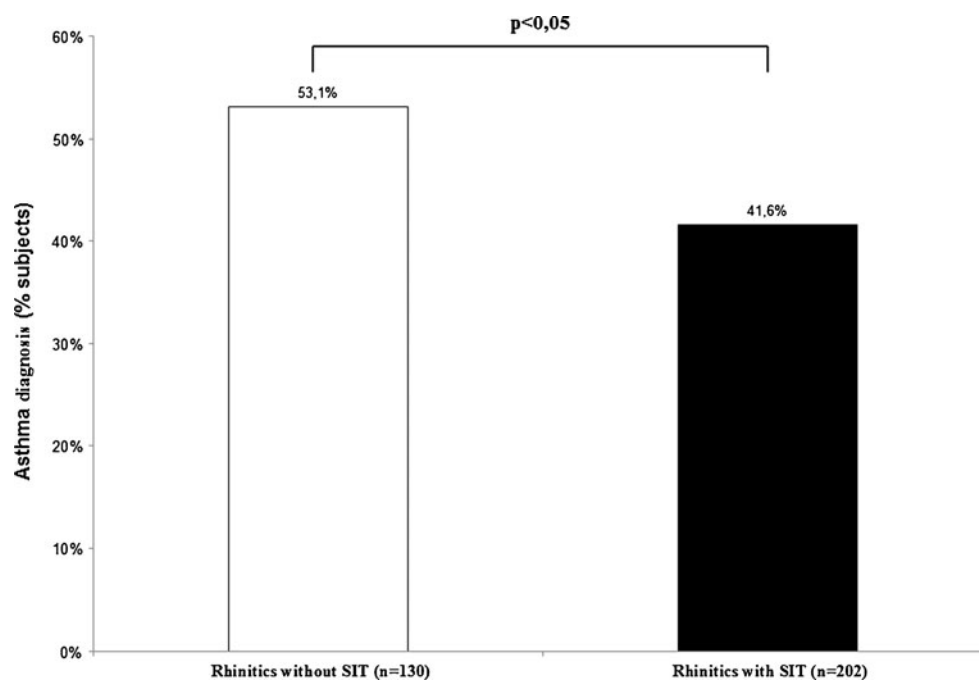
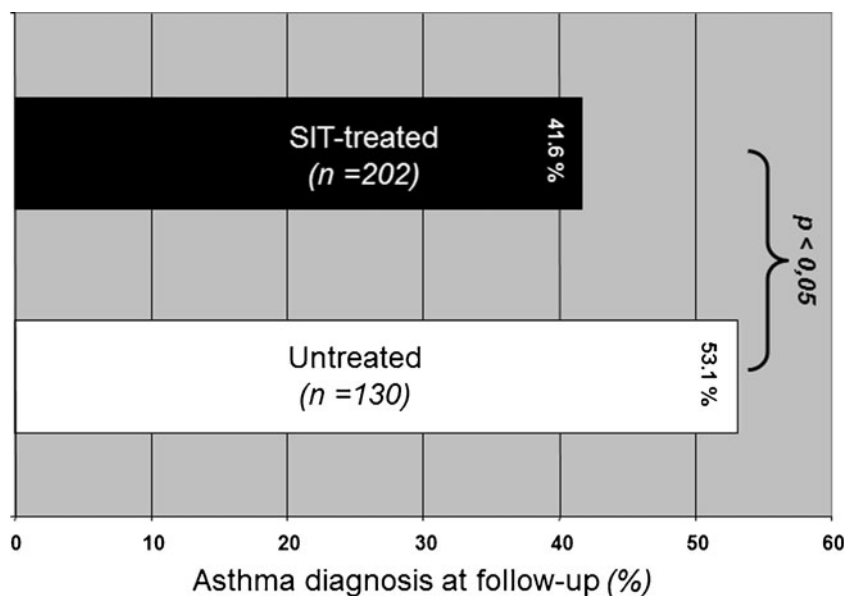


Fig. 1 SIT modifies cellular and humoral responses to allergen. The ratio of T helper 1 (T_H1)-cell cytokines to T_H2 -cell cytokines is increased after SIT, and functional regulatory T (T_{Reg}) cells are induced. The production of interleukin-10 (IL-10) by monocytes, macrophages, B cells and T cells is increased. The production of transforming growth factor- (TGF) is increased and, together with IL-10, TGF might contribute to T_{Reg} -cell function and immunoglobulin class-switching to IgA, IgG1 and IgG4.

These immunoglobulins compete with IgE for allergen binding, thereby decreasing the allergen capture and presentation that is facilitated by IgE in complex with the high-affinity receptor for IgE (FcεR1) or the low-affinity receptor for IgE (FcεRII, CD23). In addition, SIT decreases the number of mast cells/basophils and the ability of these cells to release mediators. The recruitment of eosinophils and neutrophils to sites of allergen exposure is also decreased

Fig. 2 Percentage of new onset asthma by the end of the study in specific immunotherapy (SIT) treated (*filled bar*) and untreated (*open bar*) subjects with allergic rhinitis

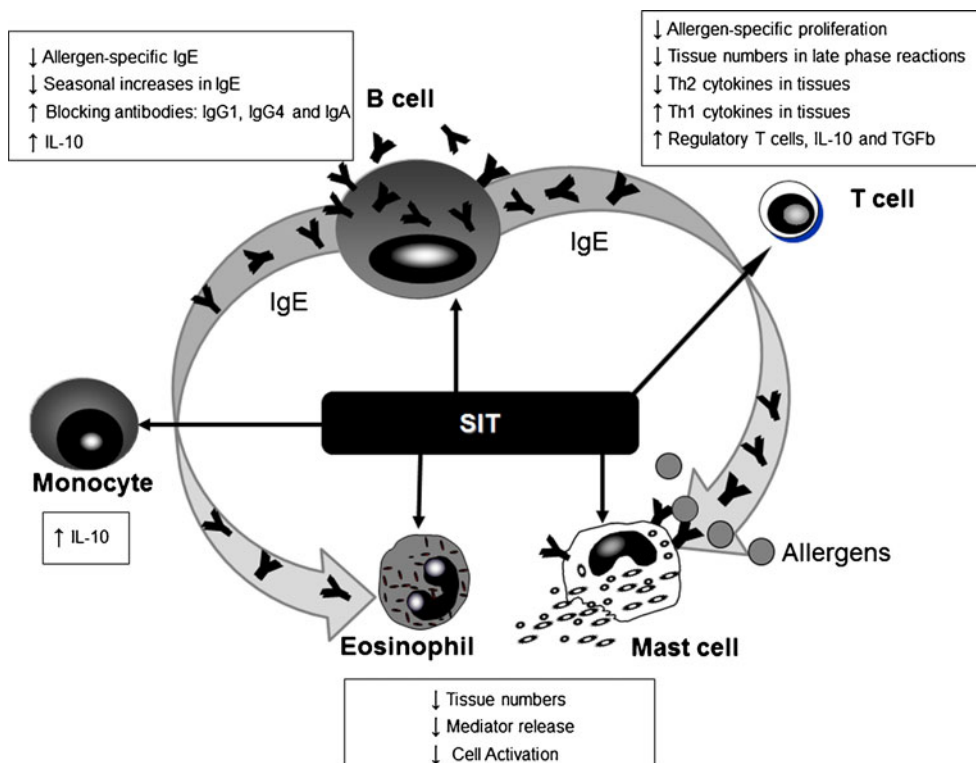


Clinical Evidence of the Role of SIT in Preventing Progression from AR to Asthma

Initial retrospective studies have demonstrated that markedly low rates of new sensitizations following SIT in mono-sensitized individuals [64–66]. In these studies the percent of SIT-treated patients who were not sensitized to a new allergen ranged from just over 45 to 75 % in contrast to 0 to just over 33 % in untreated patients. These observations have

been confirmed in two open-labelled studies [32, 67]. Inal and colleagues assessed subcutaneous SIT in 147 house dust mite monosensitized children with AR ($\pm$ asthma) over 5 years and observed that 75.3 % in the SIT-treated compared to 46.7 % in the control groups had no new sensitizations [67]. Likewise, in a larger randomised 3-year study in a similar group of children treated with sublingual SIT, only 3.1 % active compared to 34.8 % in the control group developed new sensitizations [32].

Fig. 3 Percentage of new onset asthma by the end of the study in Parietaria and house dust mite (HDM) SIT treated (*black arrows*) and untreated (*grey arrows*) allergic rhinitic subjects with positive skin prick test to Parietaria and HDM, respectively



The strongest evidence for the efficacy of SIT in reducing the onset of asthma originates from the Preventive Allergy treatment (PAT) study [29, 31, 53]. In this open-labelled, randomised study in 205 children undergoing subcutaneous SIT, the subjects were followed for up to 10 years post-treatment completion, i.e. at completion of the treatment period, and at 2-year and 10-year follow-up. As expected, there were sustained improvements in the AR symptoms over the 10-year period. Moreover, there were reported significantly fewer children developing asthma in the SIT-treated group at 3 (OR 2.52), 5 (2.68) and 10 years (OR 2.5) of treatment initiation [29, 31, 53] with a longitudinal treatment effect (adjusting for baseline BHR and asthma) over the 10-year period being statistically significant ($p=0.0075$) [53].

More evidence of the positive effect of SIT in preventing the progression from AR to asthma also comes from other longitudinal and smaller case/clinical studies [30, 38, 54, 55]. For example, a retrospective clinic-based study of 332 AR subjects over a 10-year follow-up period, showed that 53.1 % untreated compared to 41.6 % SIT-treated subjects developed asthma (OR 0.53) [38] (Fig. 2). A secondary analysis for the effects of SIT among those individuals with positive sensitivity to *Parietaria* and those with positive sensitivity to HDM clearly shows that treatment with *Parietaria* SIT reduces development of asthma in adults with allergic rhinitis, whereas treating positive HDM subjects with allergic rhinitis with HDM SIT failed to reduce the rising incidence of asthma in this subgroup (Fig. 3). In a small ($n=30$) double-blind, placebo-controlled, randomised 3-year study of subjects with *Parietaria*-induced AR reported that 14 % in the active group compared to 47 % in the control group ($p=0.056$) developed asthma following treatment with sublingual SIT [54]. In an open-labelled randomised control study over 3 years of 113 children with grass pollen-induced AR there was 3.8 times greater likelihood of developing asthma in the control group compared to sublingual SIT-treated subjects [30]. A 'real-life' case-controlled multi-centre Italian EFESO observational study which examined both adults and children with AR demonstrated that 8.5 % of the sublingual SIT-treated subjects suffered from asthma versus 20 % in the control group [55].

Although SIT may potentially avert new sensitizations and the development of asthma in AR, it is important to acknowledge that the overall quality of the current evidence is suboptimal, and that well-conducted large, long-term follow-up double-blind, placebo-controlled randomised studies are necessary. With the availability of more practical SIT formulations (e.g. tablet sublingual SIT, aqueous sublingual SIT, enteric and microencapsulated SIT preparations—which are more convenient to administer and randomise), it will be simpler to design and implement such studies. A phase 3 trial using tablet sublingual SIT, the GRAZAX Asthma Prevention (GAP) Study, is already underway with results being available by 2015 [68]. Another ongoing controlled, double-blind trial

using immunoprophylaxis for the prevention of allergic disease is the Global Prevention of Asthma in Children (GPAC) study. The goal of this phase 2 multicenter trial, is to assess whether 1 year of treatment with aqueous sublingual SIT can prevent the development of asthma and reduce the rate of allergic sensitization in high-risk children [69].

Conclusions

Although there have been significant advances in SIT therapy with clinical trials revealing its efficacy in AR and possible aversion to progressing to asthma [70, 71], the adoption of this immunomodulatory therapy is still limited in comparison to symptomatic therapies. This may be attributed to lack of awareness of the clinical benefits of SIT, its safety profile, the multiple routes of administration of currently available SIT formulations, a greater experience with conventional symptomatic medications or because of the short-term steep costs of SIT. On the other hand, there is conclusive evidence that, in pre-school children at high risk for asthma, early anti-inflammatory therapy with inhaled corticosteroids fails to modify the natural course of the disease [72–74]. However, the usefulness of SIT for the treatment of allergic individuals is suggested by the observation that when given to at-risk individuals SIT may prevent the development of allergic diseases. Hence, considering that the studies described in the literature are largely observational or uncontrolled, large well-conducted randomised clinical trials with long-term efficacy of SIT, whatever the route of administration, will be required to confirm or refute the concept that SIT may prevent progression to asthma in patients with AR.

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Compliance with Ethics Guidelines

Conflict of Interest Jaymin B. Morjaria has received honoraria for speaking and financial support to attend meetings/advisory boards from Wyeth, Chiesi, Pfizer, Merck Sharp & Dohme, Boehringer Ingelheim, Teva, GlaxoSmithKline/Allen & Hanburys, Napp, Almirall, and Novartis.

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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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- Of importance
- Of major importance

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