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Preventing progression of allergic rhinitis: the role of specific immunotherapy

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ABSTRACT

Allergic rhinitis and asthma are examples of allergic airways disease. Despite their differing symptomatology, both disorders affect the mucosal lining of the respiratory tract and are linked by common underlying cellular processes, thus, using the 'united airways' approach, they can be considered part of the same allergic disease. The conditions are often comorbid, and there is evidence to suggest that allergic rhinitis in children is a significant risk factor for subsequent development of asthma. Management strategies that target the underlying cause of allergic rhinitis in children have the potential to offer additional symptom control above that of symptomatic medications, and prevent disease progression. Specific immunotherapy (SIT) is the only currently available treatment that is proven to target the disease in this way. SIT affects the underlying cause of allergic rhinitis, producing changes in antibody responses to allergens. It has been shown to be effective in the reduction of allergic rhinitis symptoms in both children and adults, with effects being sustained for several years after treatment completion. Furthermore, a number of trials provide evidence that SIT may prevent the development of new sensitisations and asthma in children and adults with allergic rhinitis. One such open-label, randomised controlled study in children/adolescents (the Preventive Allergy Treatment Study) showed that significantly fewer patients who received 3 years of SIT for grass/birch pollen-induced allergic rhinitis had developed asthma 10 years after treatment initiation versus controls. Some clinical guidelines acknowledge this potential asthma preventive effect in children and the need for additional data from double-blind, placebo-controlled trials to support these findings.

ALLERGIC RHINITIS AND ASTHMA ARE PART OF THE SAME ALLERGIC CONDITION: 'UNITED AIRWAYS' APPROACH

Allergic airways disease encompasses a variety of symptoms and conditions that affect the mucosal lining of the airways, from the nose to the lungs.^{1–3} These symptoms/conditions vary in terms of their site of manifestation and severity, ranging from, for example, mild allergic rhinitis affecting the nose, to severe allergic asthma affecting the lungs. However, the allergic responses causing these conditions involve a shared mucosal lining, have a common lymphoid system, and also show similarities in underlying

cellular processes, including the involvement of IgE. As a result, allergic airways disease is increasingly being viewed as a continuum, rather than consisting of discrete disease entities. The rationale underlying this 'united airways' approach is shown in figure 1. Although allergic rhinitis and allergic asthma involve different regions of the respiratory mucosa, both conditions can be triggered by allergen presentation to T cells, leading to mast cell sensitisation (via cross-linking of cell surface IgE), release of inflammatory mediators, and recruitment of leucocytes (eg, eosinophils), which in turn trigger acute, and potentially chronic, allergic airways responses.^{3–7} The anatomical differences between the upper and lower airways ensure that these pathological processes manifest differently in terms of symptoms, with these cellular processes having a major effect on the vasculature surrounding the upper airways (causing rhinorrhoea, congestion, etc), while in the lower airways these processes affect the smooth muscle surrounding the bronchi, producing bronchoconstriction (causing wheezing and breathing difficulties).^{3,4}

Additional justification for a more combined approach to allergic airways disease comes from investigations showing that nasal challenge (eg, with grass pollen) can induce bronchial inflammation/responsiveness, and that segmental bronchial provocation can induce nasal inflammation, in patients with allergic rhinitis without asthma symptoms.^{3,8,9} Furthermore, patients with asthma without allergic rhinitis symptoms have been shown to have eosinophil infiltration of the nasal mucosa.¹⁰ Mechanisms proposed to connect the cellular processes in the upper and lower airways include localised airway inflammation causing a bone marrow-mediated systemic response,¹¹ a nasobronchial reflex, and functional effects such as allergic rhinitis-related congestion promoting breathing through the mouth (bypassing the nasal defences) and nasal secretions descending to the lower airways.⁴

Given these pathological links, it is unsurprising that allergic airway disorders are often comorbid, with, for example, the prevalence of allergic rhinitis being high in patients with allergic asthma.¹² In one study, the reported prevalence of allergic rhinitis in patients with asthma was approximately 80%, while in

Best practice

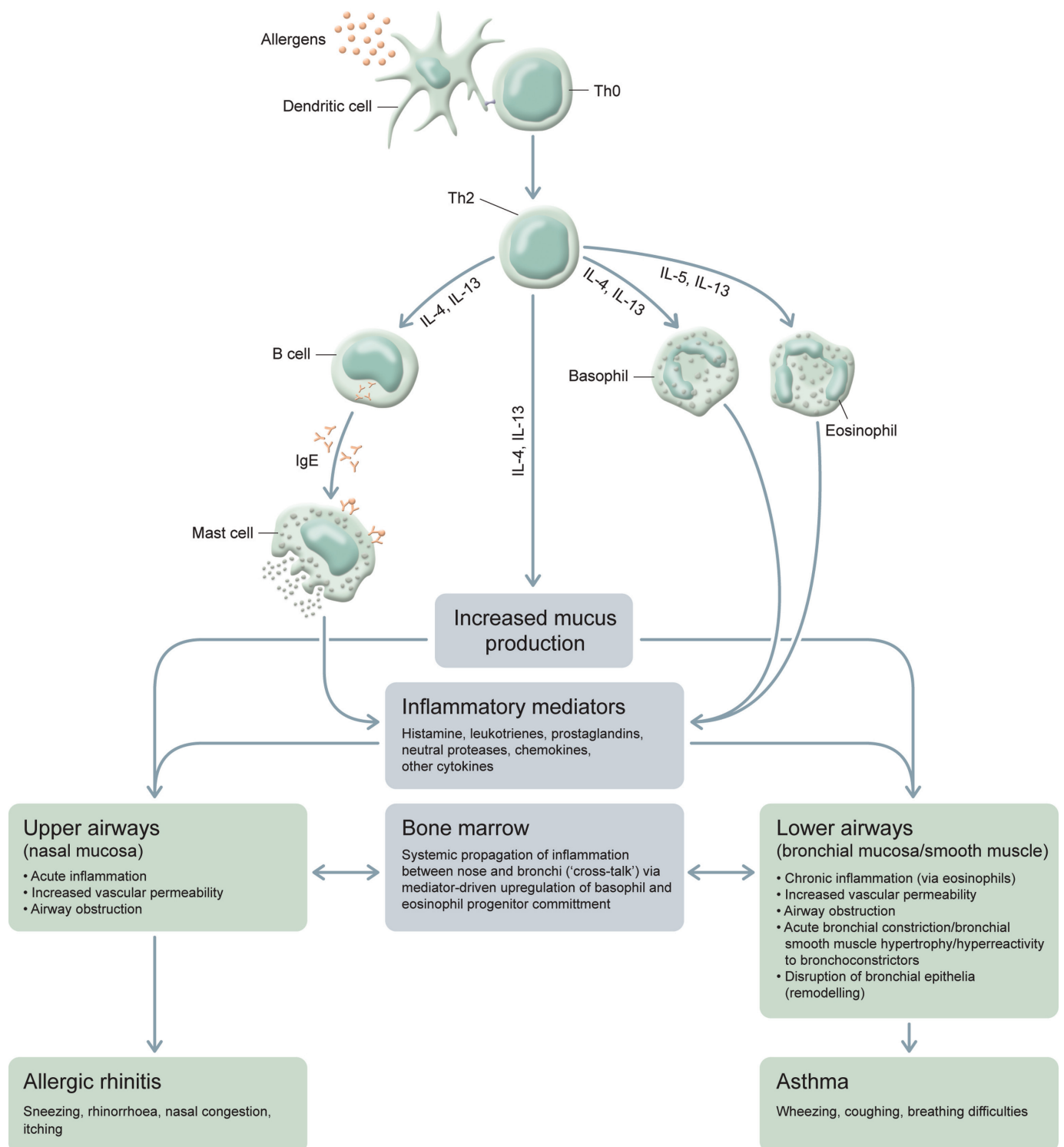


Figure 1 Common cellular processes mediate the allergic response in allergic rhinitis and asthma.^{3–7 11}

another study 100% of subjects with pollen-related allergic asthma had pollen-related allergic rhinitis.^{13 14} A recent abstract confirms this high level of comorbidity among a community-based sample of subjects with asthma.¹⁵ The close relationship/comorbidity of allergic conditions, such as that seen with allergic rhinitis and asthma, aligns with the concept of the 'allergic march': the sequential development of allergic

disease manifestations (eg, atopic dermatitis, food allergy, allergic rhinitis, asthma) during early childhood.^{12 16} While it is possible that this concept is an oversimplification, with reality involving more complex and patient-specific patterns of disease progression and comorbidity,^{17 18} it is clear that for many patients, the presence of allergic rhinitis is a risk factor for developing asthma.¹²

DISEASE PROGRESSION FROM ALLERGIC RHINITIS TO ASTHMA: CHILDHOOD AND BEYOND

The development of allergic rhinitis during childhood can represent a significant burden on quality of life, in addition to the symptomatic discomfort and practical issues associated with the condition. Health-related quality of life issues linked to childhood allergic rhinitis include poor learning performance, sleep loss, isolation from peers, emotional problems, fatigue, limitations in daily activities and family dysfunction.^{19–21} A specific example was provided by a UK-based case-control study, in which allergic rhinitis symptoms were found to be associated with dropped examination grades in students aged 15–17 years.²² Together, these findings show that allergic rhinitis is not a trivial disease in childhood. Furthermore, epidemiological studies have found that its prevalence is increasing.²³

As mentioned above, in addition to the more immediate/short-term impact of allergic rhinitis on quality of life, the presence of allergic rhinitis (in line with the allergic march) is associated with the subsequent development of asthma and new sensitisations in children^{24–30} and adults.^{29 31–35} In a longitudinal study by Burgess *et al*, childhood allergic rhinitis increased the risk of developing new-onset asthma in later life by two- to seven-fold ($p < 0.01$), with the greatest risk of developing asthma being between 7 and 12 years of age.²⁹ Childhood allergic rhinitis also increased the likelihood of asthma persisting from childhood into middle age.²⁹ These findings are supported by the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines from 2008, which clearly state that allergic rhinitis should be considered as a risk factor for asthma.¹² Furthermore, it has been demonstrated that the presence of childhood asthma can, in turn, ultimately result in severe pneumopathy (eg, persistent wheezing) in adulthood.³⁶

Therefore, although allergic rhinitis is often perceived as a relatively minor condition, it can have a notable detrimental effect on the lives of children and may also herald the development of even more severe respiratory pathology.

PREVENTING THE PROGRESSION OF ALLERGIC RHINITIS: PHARMACOLOGICAL OPTIONS

The potential for allergic rhinitis treatments to reduce the symptoms of comorbid asthma has been reported in some studies. For example, in a retrospective cohort study of patients with allergic rhinitis and asthma (aged 12–60 years; $n = 4944$), treatment for allergic rhinitis was shown to halve the risk of asthma-related events (eg, hospital visits).³⁷ However, since allergic rhinitis is associated with the development of new asthma cases, it is also of interest to consider whether early treatment of allergic rhinitis may, in fact, prevent subsequent disease progression to allergic asthma.³⁸

Pharmacological options currently available for the treatment of allergic rhinitis consist of

symptomatic medications (eg, oral antihistamines, nasal corticosteroids, decongestants, leukotriene receptor antagonists) and specific immunotherapy (SIT).¹² The symptomatic medications address the symptoms of allergic rhinitis by targeting specific aspects of the allergic response, for example, reducing inflammation or itchiness. In contrast, SIT treats the underlying cause of allergic rhinitis, reducing the need for symptomatic medications and producing a reduction in symptoms during treatment, with these effects being sustained after the completion of treatment.³⁹ The SIT mechanism of action is not fully understood, but is based upon the specific repeated administration of allergens to allergic individuals in order to activate immunomodulatory mechanisms,⁴⁰ thus reducing an individual's sensitivity to an allergen (ie, inducing immune tolerance). This approach is thought to stimulate the production of regulatory T cells, which directly inhibit type 2 T helper cells, thereby reducing mediator release and the resulting allergic response (see figure 1).^{5 6 41 42} Reductions in the IgE antibody response and upregulation of the allergen-specific IgG antibody response (hypothesised to block IgE) have also been observed with SIT treatment, although the clinical impact of these effects has not been fully elucidated.^{5 41 43} Thus, in contrast to symptomatic medications, it is clear that SIT has the potential to affect the underlying allergic disease processes. Given the united airways concept, and the common pathological processes leading to allergic rhinitis and asthma, it is therefore worth considering whether SIT would be well placed to slow or even halt the progression of allergic rhinitis to asthma and new sensitisations. Evidence relating to these considerations is presented in the remainder of this article. Although not the focus of this article, we should also briefly consider the effects of allergen avoidance and symptomatic treatments on disease progression: there is no direct evidence that either intervention prevents the progression of allergic rhinitis to asthma, although there is limited positive and negative evidence for the ability of these interventions to prevent the development/worsening of asthma symptoms in a broader context.^{44–54} Further research is thus required.

CLINICAL EVIDENCE: THE ROLE OF SIT

Despite advances in SIT in recent years, with clinical studies demonstrating its efficacy in allergic rhinitis (see below) and asthma,^{55 56} the adoption of disease-modifying immunomodulatory therapy in allergy treatment is still limited compared with conventional symptom-relieving medications. This may be because of a lack of awareness of the clinical effects, safety profile and administration routes of current SIT formulations, a greater familiarity with the more traditional symptomatic medications, or because of the short-term cost implications of SIT. Whichever, if SIT does offer a safe and effective opportunity to improve disease

outcomes and progression, then careful consideration needs to be given to its wider and earlier use (eg, during childhood), before disease progression and further sensitisations occur.

SIT can be administered to patients subcutaneously (subcutaneous immunotherapy, SCIT) via a course of supervised injections, or sublingually (sublingual immunotherapy, SLIT) via daily drop-based formulations and allergy immunotherapy tablets (AITs), which the patient may administer at home. The efficacy of SCIT for both allergic rhinitis and asthma is long-established, but the development of SLIT in the 1980s represented an important advance in terms of improved safety (overcoming concerns regarding systemic side effects associated with subcutaneous administration) and convenience for patients.^{12 38} SLIT is currently used in countries across Europe, Asia, Australia and South America,³⁸ and several position papers have outlined the history and current evidence surrounding all SIT administration modalities.^{12 38 57}

Effects on existing allergic rhinitis

Overall, clinical data have shown that SIT (SCIT and SLIT) are efficacious against the symptoms of allergic rhinitis.^{12 58 59} A 2003 Cochrane Review that performed a meta-analysis of 22 randomised, controlled trials (RCTs) of SLIT for allergic rhinitis found significant reductions in symptoms (standardised mean difference (SMD) -0.42; $p=0.002$) and symptomatic medication requirement (SMD -0.43; $p=0.00003$) in the overall population (adults and children).⁵⁹ Since the Cochrane Review, a number of additional studies have been published that support its findings.^{27 60–62} There were insufficient data in the Cochrane Review to make a conclusion regarding a specific effect in children,⁵⁹ due to a limited number of paediatric studies in allergic rhinitis at that time (2003). However, a later meta-analysis that included 10 paediatric studies of SLIT in allergic rhinitis, found significant reductions in symptoms (SMD -0.56; $p=0.02$) and medication use (SMD -0.76; $p=0.03$).⁶³ In addition, more recent data from individual studies have shown grass AITs to be highly effective in children with grass pollen-induced allergic rhinitis (see below).^{64 65} Significant heterogeneity was observed in the results of both the adult and childhood allergic rhinitis meta-analyses, which the authors concluded was likely to be due to the wide range of different scoring systems used in allergic rhinitis investigations.^{59 63}

Other study outcomes have indicated that SIT (SCIT, AITs) can improve quality of life scores (on Juniper's Rhinoconjunctivitis Quality of Life Questionnaire, RQLQ⁶⁶) by up to one third (vs placebo) in patients with pollen-induced allergic rhinitis.^{62 67 68} The grass AIT, GRAZAX (ALK-Abelló) has demonstrated a greater effect on quality of life than antihistamine treatment alone.⁶⁷

Regarding longer-term efficacy outcomes, studies show that the clinical effects of SIT are sustained for several years after the completion of treatment. For example, symptom scores and medication use have remained significantly reduced (vs control groups) for up to 12 years after the completion of SIT in children with allergic rhinitis and/or asthma.^{28 69 70} Treatment in adults with allergic rhinitis and/or asthma has shown similar effects, with studies reporting that symptoms stabilise or in some cases, further decrease, 3–6 years after completion of SCIT.^{71 72} The grass AIT also has a sustained effect 1 year after the completion of a 3-year treatment period in adults, as demonstrated by the sustained reduction in symptoms and need for symptomatic medications, and an improved quality of life.^{39 73} Further study on the long-term effects of SIT in children and, in particular, the impact of this treatment on quality of life in childhood, would be valuable.

Preventing disease progression

In addition to the effect of SIT during and after the completion of treatment, there is some evidence that SIT may actively prevent the development of new sensitisations and asthma in children and adults (table 1).^{24–28 34 69 70 74–77}

A number of studies suggest that SIT can reduce the development of new sensitisations in patients with allergic rhinitis (table 1).^{27 28 74–76} For example, at the end of the 3-year treatment period of an open-label, RCT of children with allergic rhinitis ($\pm$ intermittent asthma, $n=216$), new sensitisations developed in approximately 3% of SIT-treated patients (single allergen SLIT for mites, grasses, birch or *Parietaria*) compared with approximately 35% of the control group (OR 0.06).²⁷ A non-randomised, open-label study of children with allergic rhinitis ($\pm$ asthma, $n=147$) revealed a similar significant effect with SCIT for mite allergy over a 5-year treatment period.⁷⁵ In terms of preventing asthma development, a small ($n=30$) double-blind, randomised, placebo-controlled trial in adults with *Parietaria*-induced allergic rhinitis showed that at the end of the 3-year treatment period fewer patients developed asthma in the SIT-treated group than in the control group (14% vs 47%; $p=0.056$).⁷⁷ In another RCT (open-label) involving 3 years of SLIT treatment in children with grass pollen-induced allergic rhinitis ($n=113$), the development of asthma was 3.8 times more frequent in the control group than in the SLIT-treated group.²⁵

Importantly, long-term follow-up studies (non-randomised) have also observed the apparent preventive effect of SIT on new sensitisations/asthma up to 12 years after completion of treatment.^{28 69 74 76} This is a key outcome, as it discounts the possibility that the observed preventive action of SIT is simply due to an effective treatment of symptoms during the active treatment period. The strongest evidence for this effect

Table 1 Summary of clinical trials demonstrating the preventive effects of specific immunotherapy in the treatment of allergic rhinitis and/or asthma

Authors/ study	Population	Diagnosis	Study design/type	Main efficacy outcomes for SIT group at end of study	Preventive effects for SIT group at end of study
Novembre <i>et al</i> , 2004 ²⁵	Children, 5–14 years (n=113)	AR (grass) (<3 episodes asthma/season)	Randomised, controlled, * open, 3-year SLIT study Standardised 5-grass mix pollen extract, sublingual drops (ALK-Abelló)	End of 3-year treatment period: Medication scores: reduction from baseline (p=0.02 vs control) Symptom scores: no difference vs control	End of 3-year treatment period: Asthma development: less frequent than in control group (OR 3.8)
Pajno <i>et al</i> , 2001 ¹⁴	Children, 5–8 years (n=138)	Asthma±rhinitis (HDM)	Non-randomised, controlled, * open, 6-year SCIT study (3 years + 3 years after treatment completion) Standardised depot preparation of 50% <i>Dermatophagoides pteronyssinus</i> and 50% <i>Dermatophagoides farinae</i> (Alutard SQ, ALK-Abelló)	–	6-year follow-up (3 years after end of SCIT): New sensitisations: 24.6% vs 67.7% control (p<0.0002)
Eng <i>et al</i> , 2006 ²⁸	Children, 5–16 years (n=28)	Severe AR (grass)	Non-randomised, controlled, * open 15-year SCIT (allergoid) study (3 years + 12 years after treatment completion) Grass pollen depot allergoids (Allergopharma)	15-year follow-up (12 years after end of SCIT): Symptom scores: significant reduction (p<0.03 vs control) Combined symptom and medication scores: significant reduction (p<0.03 vs control)	15-year follow-up (12 years after end of SCIT): Seasonal asthma: lower prevalence (p=0.08 vs control) New sensitisations: 58% vs 100% control (p<0.05)
Di Rienzo <i>et al</i> , 2003 ⁶⁹	Children, 3–17 years (n=60)	AR and/or mild to moderate asthma (HDM)	Non-randomised, controlled, * open, parallel-group, 10-year prospective SLIT study (4–5 years + 4–5 years after treatment completion) Standardised 2-species mix HDM extract, sublingual drops (ALK-Abelló)	10-year follow-up (5 years after end of SLIT): Asthma medication use: 9% vs 96% control (p<0.001)	10-year follow-up (5 years after end of SLIT): Asthma development: significantly less (p<0.001 vs control) No significant difference in new sensitisations
Marogna <i>et al</i> , 2008 ²⁷	Children, 5–17 years (n=216)	AR±intermittent asthma	Randomised, controlled, * open, 3-year SLIT study Standardised birch, grass, <i>Parietaria</i> or HDM extracts, sublingual drops (Anallergo)	End of 3-year treatment period: Symptom plus medication scores: reduced from baseline (p<0.001 vs control)	End of 3-year treatment period: New sensitisations: 3.1% vs 34.8% control (OR 0.06) Mild persistent asthma in children with asthma at baseline: 1.5% vs 28.8% control (OR 0.04)
Polosa <i>et al</i> , 2004 ⁷⁷	Adults, 20–54 years (n=30)	AR (no asthma) (<i>Parietaria</i>)	Randomised, double-blind, placebo-controlled, 3-year SCIT study Standardised <i>Parietaria judaica</i> extract, subcutaneous injection (Alutard SQ, ALK-Abelló)	End of 3-year treatment period: Symptom scores (median): significant difference in favour of SCIT vs control (p=0.001) Medication scores: significant difference in favour of SCIT vs control (p=0.002)	End of 3-year treatment period: Asthma development: 14% vs 47% control (p=0.056)
Reha and Ebru, 2007 ⁷⁶	Children, 4–15 years (n=107)	Asthma and/or AR (HDM or grass)	Non-randomised, controlled, * 9-year SCIT study (4 years + 5 years after treatment completion) Standardised HDM-mix or grass-mix extracts, depot injection (Phostal, Stallergènes)	9-year follow-up (5 years after end of SCIT): Symptom scores: significant decrease in both groups	9-year follow-up (5 years after end of SCIT): New sensitisations: HDM 18.6%, grass 23.1%, control group 39.2% (p=0.033 HDM/grass vs control)
Inal <i>et al</i> , 2007 ⁷⁵	Children, 6–16 years (n=147)	AR and/or asthma (HDM)	Non-randomised, parallel-group, open, controlled, * 5-year study of SCIT as adsorbed and aqueous extracts Standardised HDM adsorbed extracts, depot injection (Alutard SQ, ALK-Abelló; NovoHelix Depot, Allergopharma; APSI Retard, Stallergènes); aqueous extracts (Greer Laboratories)	End of 5-year treatment period: Medication scores: significant reduction in asthma medication (p<0.05), but not AR medication, vs baseline with SCIT Control group showed no significant changes vs baseline	End of 5-year treatment period: New sensitisations: 24.7% vs 53.3% (p=0.002) Correlation between new sensitisation development and higher atopy scores (p=0.002), AR medication scores (p=0.008) and asthma (p=0.013)
Möller <i>et al</i> , 2002 (PAT study) ²⁴	Children, 6–14 years (n=205)	Seasonal AR (grass/birch)	Randomised, controlled, * open, 3-year SCIT study, with 5- and 10-year follow-up Standardised grass and/or birch extracts, depot injections (Alutard SQ, ALK-Abelló) or aqueous extracts (Aquaen SQ, ALK-Abelló)	End of 3-year treatment period: VAS rhinitis scores: improvement from baseline (p<0.01 vs control) VAS conjunctivitis scores: improvement from baseline (p<0.05 vs control) 5-year follow-up (2 years after end of SCIT): VAS rhinitis scores: improvement from baseline (p<0.01 vs control) VAS conjunctivitis scores: improvement from baseline (p<0.001 vs control)	End of 3-year treatment period: Asthma development: of those without asthma at baseline, lower incidence of new asthma in SCIT group vs control (OR 2.52) 5-year follow-up (2 years after end of SCIT): Asthma development: of those without asthma at baseline, lower incidence of new asthma in SCIT group vs control (OR 2.68) Asthma scores: significantly worse at 5 years for control. No significant change for SCIT group
Niggemann <i>et al</i> , 2006 (5-year follow-up) ²⁶	5-year follow-up (n=183)	(No asthma needing daily treatment)		10-year follow-up (7 years after end of SCIT): VAS rhinitis scores: improvement from baseline (p<0.05 vs control) VAS conjunctivitis scores: improvement from baseline (p<0.05 vs control)	10-year follow-up (7 years after end of SCIT): Asthma development: of those without asthma at baseline, lower incidence of new asthma in SCIT group vs control (OR 2.5)
Jacobsen <i>et al</i> , 2007 (10-year follow-up) ⁷⁰	10-year follow-up (n=147)				

*Control group received symptomatic medication only for the study period.

AR, allergic rhinitis/rhinoconjunctivitis; HDM, house dust mite; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; VAS, visual analogue scale.

comes from the Preventive Allergy Treatment (PAT) Study – a large (n=205), open-label, RCT – which followed children/adolescents (aged 6–14 years at study start) for up to 7 years after completion of 3 years of treatment with SCIT for seasonal grass and/or birch pollen-induced allergic rhinitis (ie, 10-year follow-up).^{24 26 70} As well as finding that significant improvements in allergic rhinitis were maintained over this period, the study found that significantly fewer patients in the SCIT-treated group had developed asthma at 3 years (OR 2.5), 5 years (OR 3.1) and 10 years (OR 2.5) after childhood treatment initiation.⁷⁰ Interestingly, despite these asthma findings, there was no significant bronchial hyper-responsiveness (or difference between groups) at either the 5- or 10-year follow-up (although there was a significant difference between groups at the end of the 3-year treatment period).⁷⁰ The study authors suggest that this could be due to a natural improvement from childhood to adulthood.⁷⁰ The longitudinal preventive effect of SIT in terms of asthma development (controlled for bronchial hyper-responsiveness and asthma status at baseline) across the 10 years of this study was found to be statistically significant ($p=0.0075$).⁷⁰

Although current evidence supports the proposal that SIT may prevent the development of new sensitisations and disease progression in allergic rhinitis, it should be noted that the quality of this evidence is varied – several studies were non-randomised and most were open-label. Open-label designs are not unexpected for investigations of this type, due to the practicalities of implementing blinded trials over long follow-up periods, however, the World Allergy Organization (WAO) guidelines recommend that all SIT trials should be randomised, double-blind and placebo controlled.⁷⁸ There are ethical issues associated with this design in paediatric studies, such as the use of the invasive placebo treatment that is required to simulate SCIT, however, with the development of sublingual formulations this hurdle can be overcome. Thus, there is a clear need and opportunity for large, well-designed, double-blind, placebo-controlled, randomised trials, with post-treatment follow-up, in order to provide robust substantiation of current evidence. One such trial – the GRAZAX Asthma Prevention (GAP) Study – is currently underway. The GAP study is scheduled to run from 2010 to 2015 and will be a double-blind, randomised, parallel-group, placebo-controlled, multicentre trial, with a target population of over 600 children aged 5–12 years with grass-pollen induced allergic rhinitis without asthma. Patients will receive grass AIT treatment for 3 years, and will be followed for a further 2 years, with the aims of assessing the preventive effect of this treatment on asthma development, and determining if this effect is sustained after the completion of treatment.

Safety

SCIT has been associated with both local and systemic side effects including rare occurrences of adverse events requiring epinephrine, but when administered in a controlled, clinical setting, the risk is greatly minimised.^{12 58} SLIT is considered to provide a more favourable tolerability profile than SCIT, with studies demonstrating safety in both children and adults.^{12 63} One evidence-based study that directly compared the safety of grass SCIT (four preseasonal injections; n=595) with a grass AIT (daily; n=1011) concluded that both were safe treatments for allergic rhinitis, although systemic side effects occurred in fewer patients receiving the AIT (3%; headache) compared with SCIT (11%; headache, conjunctivitis, rhinitis).⁷⁹ The 2003 Cochrane Review meta-analysis of SLIT studies demonstrated the absence of systemic adverse events, with minor local side effects consisting of itching and swelling of the oral mucosa (generally not considered clinically significant). In addition, in 2006, a meta-analysis of paediatric studies reported that SLIT was well tolerated, with almost all adverse events classed as mild, and no fatal or severe systemic reactions.⁶³ The Practical Allergy (PRACTALL) consensus report comments that due to these contrasting tolerability profiles, effective SLIT may be an attractive alternative to SCIT for children, parents and physicians alike.⁸⁰

LATEST DEVELOPMENTS IN SIT

New formulations

As mentioned earlier, in addition to SCIT and sublingual drop immunotherapy, SIT for grass pollen allergy is now available as sublingual tablets for home administration (AITs) as both single species *Phleum pratense* allergen extract tablets (GRAZAX, ALK-Abelló) and 5-grass mix pollen allergen extract tablets (Oralair, Stallergènes). Both grass AITs have shown efficacy and favourable tolerability profiles in adults with allergic rhinitis in the first pollen season of treatment.^{81 82} In addition, GRAZAX is the first grass AIT to demonstrate sustained effects after the completion of treatment: highly significant symptomatic improvement, reduction in medication use, and an improved quality of life, alongside immunological changes and a good tolerability profile.^{39 73} Further, recently published data from two 1-year paediatric studies (5–16/17 years) provide evidence for significant efficacy and favourable tolerability of the grass AITs in children with allergic rhinitis.^{64 65} The two studies had similar designs and patient populations, and the primary efficacy outcome measures were highly comparable when the same pollen season definition was used (≥ 30 grains/m³).^{64 65 83} Both GRAZAX and Oralair produced a significant reduction in rhinoconjunctivitis symptoms over the pollen season (≥ 30 grains/m³), with a 28% reduction in

Table 2 Clinical guideline conclusions on the preventive/persistent effects of specific immunotherapy

Guideline	Statements
ARIA/WHO*	Allergen-specific immunotherapy may alter the natural course of allergic diseases, appears to be effective several years after its cessation, and appears to reduce the development of new sensitisations. ¹² Administered to patients with rhinitis, immunotherapy appears to reduce the development of asthma (secondary prevention of asthma). ¹² Moreover, sublingual immunotherapy in young children with AR may possibly prevent later development of asthma. ¹² Various studies have provided evidence that treatment of allergic rhinitis with specific immunotherapy, either sublingual or subcutaneous, can reduce bronchial hyper-responsiveness and may prevent asthma. ⁹⁶
WAO†	Allergen-specific immunotherapy may alter the natural history of respiratory allergy by preventing the onset of new skin sensitisations and/or reducing the risk of asthma onset. ³⁸ Two randomised, open, controlled studies suggest that sublingual immunotherapy reduces the risk of asthma onset in children with rhinitis. ³⁸ Two randomised, open studies show that sublingual immunotherapy reduces the onset of new allergen sensitisations. ³⁸ One randomised, double-blind, placebo-controlled trial, and one non-randomised, prospective study suggest the persistence of the clinical effects of sublingual immunotherapy for 3–5 years after treatment completion. ³⁸
PRACTALL‡	The effect of immunotherapy appears to continue after treatment has stopped, resulting in prolonged clinical remission of allergic rhinitis symptoms. ⁸⁰ Specific immunotherapy can prevent sensitisation to other allergens. It can also improve asthma, prevent progression from allergic rhinitis to asthma, and reduce the development of asthma in children with seasonal allergies. ⁸⁰ The combination of specific immunotherapy with other therapies allows for a broad therapeutic approach that addresses the pathophysiological mechanism of allergy with the aim of making patients as symptom-free as possible. ⁸⁰
iPAC§	Subcutaneous immunotherapy has the potential for preventing the development of asthma in children with allergic rhinoconjunctivitis and some studies also indicate a preventive effect as regards new sensitivities. ⁸⁴

*Allergic Rhinitis and its Impact on Asthma (ARIA)/World Health Organization (WHO).

†World Allergy Organization (WAO) Position Paper 2009 on sublingual immunotherapy.

‡Practical Allergy (PRACTALL) consensus report on the diagnosis and treatment of asthma in childhood.

§International Pediatric Allergy and Asthma Consortium (iPAC).

AR, allergic rhinitis.

mean symptom scores (vs placebo) achieved with both treatments.^{64 65 83} Interestingly, the immunological effect of GRAZAX, as measured by changes in IgG₄ levels from baseline, are similar in both children and adults.⁶⁴ These results support the opinion that the paediatric use of grass AITs may be a valuable treatment option in the future.

The availability of grass AITs is an important development. The significant effect of the grass AIT during and after treatment, patient convenience and a favourable tolerability profile compared with SCIT, offers the possibility of many more patients benefitting from SIT treatment. The PRACTALL consensus report recognises SLIT as an appealing alternative to subcutaneous injections for children.⁸⁰ However, a reliance on patient adherence to daily dosing schedules may raise its own challenges.

Clinical guidelines

Support from the current clinical guidelines in relation to the use of SIT, and its potential role in allergy prevention, are summarised in table 2. Overall, the ARIA guidelines found good evidence that SIT is clinically effective in allergic rhinitis, shows long-term efficacy and improves quality of life.¹² Further, both the ARIA guidelines and the WAO Position Paper 2009 comment that SLIT in children with allergic rhinitis may prevent later development of asthma.^{12 38} More specifically, the international Pediatric Allergy and Asthma Consortium (iPAC) acknowledge the long-term preventive potential of subcutaneous administration of SIT in children with allergic rhinitis, while also highlighting the need for more long-term, randomised studies investigating the use of SCIT and SLIT in children.⁸⁴

ECONOMIC CONSIDERATIONS

In addition to the many clinical considerations, the presence and progression of allergic airways disease can have a considerable economic impact. While both allergic rhinitis and asthma are individually associated with substantial economic burdens, comorbid allergic rhinitis and asthma are associated with even greater costs.^{85–87} Specifically, children with comorbid allergic rhinitis and asthma incur significantly greater prescription costs and experience more GP visits and hospitalisations for asthma than children with asthma alone.⁸⁵ As described above, SIT appears to reduce the risk of asthma development in patients with allergic rhinitis, and offers the potential for long-term remission of allergic rhinitis, which would be expected to bring notable cost reductions.

Although SIT is more expensive than symptomatic medications for allergic rhinitis, if the projected reductions in allergic rhinitis and asthma costs in the future are taken into account, it should become a cost effective approach. Economic analyses examining this proposal have shown SIT to be cost-effective in the treatment of grass/mite allergy in terms of quality-adjusted life years (QALYs), as well as improving psychological well-being, reducing time missed from work and limiting health insurance costs, as compared with standard symptomatic medication in Europe.^{88–91} Adding to this, a US study highlighted the economic potential of early treatment with SIT in children with allergic rhinitis, producing significantly lower healthcare costs per patient (US\$3247 vs US\$4872 in matched controls with allergic rhinitis but not receiving SIT; $p < 0.001$) over an 18-month period.⁹² Over a 3-year treatment period, recent European economic evaluations have also found SLIT to be

less expensive than SCIT for the treatment of allergic rhinitis, from a payer, patient and societal perspective.^{93 94}

CONCLUSION

Current data suggest that early/childhood intervention in the allergic rhinitis treatment pathway might prevent disease progression to other respiratory disorders such as asthma. Disease-modifying treatment with SIT is one of the best recent advances towards achieving this goal. Further, the recent availability of SLIT, including AITs, potentially offers more paediatric allergic rhinitis patients a causal therapy that is suitable for home administration. Thus, the future for the treatment of respiratory allergies may lie in shifting the focus from the current approach, as recommended in the guidelines (ie, symptomatic medication as first-line, and adding SIT if there is inadequate control) to one where everyone is assessed for suitability for the use of SIT as a first-line treatment (ie, initiated early).⁹⁵ In addition to the possible direct preventive benefits, we speculate that this change in approach would also reduce future treatment costs and produce indirect societal benefits to parents and children (in terms of days off work/school, reduced health insurance costs, etc).

To support this approach, further robust evidence from double-blind, randomised, placebo-controlled trials should be obtained regarding the long-term efficacy and preventive effects of the sublingual/tablet-based forms of SIT in children. Specific investigations of the effect of SIT on quality of life in children would also be valuable in order to illustrate the clinically meaningful benefits of early therapy in this patient population.

Search criteria The studies included in this review were selected based on their perceived quality and relevance to the topic, following a collaboration between the authors and the review sponsor, ALK-Abelló A/S. No formal search criteria were employed in study selection.

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