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ALLERGEN IMMUNOTHERAPY FOR THE CONTROL OF ALLERGIC RHINOCONJUNCTIVITIS

Allergen immunotherapy (AIT) has been available for over 100 years as a unique method of treating various allergic conditions, most efficaciously allergic rhinitis/rhinoconjunctivitis, allergic asthma and venom allergy. First developed by Noon et al in 1911, this therapy is an attractive option for patients suffering from these chronic conditions due to its potential for disease-modification.[1] As opposed to avoidance measures and other pharmacotherapies, patients on immunotherapy can, in some cases, achieve long-term benefits after 3-5 years of treatment due to the induction of allergen tolerance.[2, 3] This article will focus primarily on patients with allergic rhinitis/rhinoconjunctivitis.

AIT is currently available in 2 forms to treat allergic rhinitis: sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT). Both therapies provide specific advantages and disadvantages, and clinicians and patients should choose which approach is best through shared decision-making. AIT is indicated in any patient (usually ≥ age 5) who has IgE-mediated rhinoconjunctivitis which is not adequately controlled with avoidance measures and pharmacotherapy, or in those who are intolerant to these therapies due to adverse events.[4-7] In general, immunotherapy is contraindicated in patients with severe or unstable asthma (FEV1 <70% in adults, FEV1 <80% in children), patients on beta-blockers (ACE inhibitors are a relative contraindication), pregnant patients (de novo AIT; if on maintenance they can continue) and those with open lesions of the oral mucosa or eosinophilic esophagitis (SLIT only).[5, 8-12]

BASIC IMMUNOLOGY AND BIOMARKERS

The immunological changes with immunotherapy have been well-documented. With chronic use, there is a decrease in IgE-dependent activation of mast cells, reduction in tissue eosinophilia and a shift to the T-regulatory and Th1 immune pathways.[13-21] These changes result in a reduction in the number of antigen-specific T cells and an increase of serum specific IgG4, IgG and IgA antibodies which prevent Th2 activation, IgE-complex formation and mast cell degranulation.[7, 22-24] IL-10-producing regulatory B cells and the associated neutralizing antibodies likely contribute to the long-term benefit seen with this therapy.[25-29] Finally, the innate immune system also plays a role, with Th2 dendritic cells and innate lymphoid cells regulated by thymic stromal lymphopoietin and IL-33 activated in these patients.[30]

Biomarkers can be used to predict response to AIT. Many biomarkers have been studied, with the more commonly examined biomarkers being serum-specific IgE and the serum-specific IgE: total IgE ratio, IgG4 antibodies and T cells (both Th2 and T regulatory).[16-19, 30-38] The effects that AIT has on these biomarkers are summarized in **Table 1**.[7] Antibodies are the easiest to measure as most labs offer enzyme-linked immunosorbent assays (ELISA).

Biomarker	Effect of AIT
Serum specific IgE	Transient increase followed by blunting of seasonal increase[30-34]
Serum specific IgE: total IgE ratio	A cut-off of 16.2% predicted benefit of AIT[35,36]
Serum specific IgG1 and IgG4	10-100 fold increase reported. IgG4 correlated with outcome[37,38]
T regulatory cells	Increased following AIT[16,17,19]

Table 1. Change in biomarkers associated with AIT.[7]

SUBCUTANEOUS IMMUNOTHERAPY AND SHORT-TERM BENEFITS

SCIT is a well-established treatment option for patients with allergic rhinitis. Allergists have the option of offering pre-seasonal (alum-based) immunotherapy for pollen sensitized patients vs. perennial immunotherapy which is available for many allergens (i.e. moulds, dust mites, pollens, animals). SCIT is usually given as weekly (or twice-weekly) injections for the 'build-up' phase and then dosed every 2-4 weeks for the maintenance phase of therapy. The short-term effectiveness of SCIT has been well-documented in a meta-analysis[39] based on 51 studies, in which it was found to be moderately effective at reducing allergy symptoms in the short-term with improvement in both seasonal allergy sufferers and perennial allergy sufferers. This effect was demonstrated in both children and adults. For medication scores, a similar benefit was noted based on an analysis of 46 studies. Both pre-/co-seasonal pollen regimens versus continuous treatment for pollens, SCIT improved symptom and medication scores.[39] Pre/co seasonal pollen regimens refer to the initiation of SLIT for grass, birch and ragweed pollen for the period involving a few months before the pollen season with continuation of therapy until the end of the pollen season. The standard mean differences (SMD) are summarized in **Table 2** with values further from 0 indicating a greater reduction and effect size. Significant values not crossing a 0 confidence interval are highlighted in red.

	Overall (Seasonal and Perennial allergens)	Seasonal Allergens	Perennial Allergens	Pre/co-seasonal pollen regimes	Continuous treatment for pollens
SMD Symptom Scores	-0.65 (95% CI -0.86, -0.43)- 51 studies	-0.49 (95% CI -0.72, -0.27)	– 1.59 (95% CI -2.44, -0.74) – **based on only one study**	−0.51 (95% CI −0.63, −0.38)	−0.69 (95% CI −1.09, −0.29)
SMD Medication Scores	−0.52 (95% CI −0.75, −0.29	−0.77 (95% CI−1.28, −0.25)	−0.27 (95% CI −1.01, 0.48) – **based on only one study**	−0.40 (95% CI −0.56,−0.25)	−1.23 (95% CI −2.34, −0.12)

Table 2. SMD in symptom and medication scores for seasonal versus perennial allergens and continuous vs. pre/co-seasonal pollen regimes with SCIT.[39]

SUBLINGUAL IMMUNOTHERAPY AND SHORT-TERM BENEFITS

SLIT is the newest form of therapy, having been approved in Canada in 2012 in the form of grass pollen tablets. Currently, SLIT tablets are available to treat patients sensitized to birch tree pollen, grass pollen, ragweed pollen and dust mites (**Table 3**). SLIT drops are also utilized by some allergists but these have less robust evidence and no long-term or sustained efficacy data.[40] Pollen tablets are usually given pre and co-seasonally and dust mite SLIT is administered perennially (on a daily basis for both). The benefits of SLIT vs. SCIT include convenience of dosing (at-home dosing other than the first administration in office), a lower likelihood of systemic reactions than SCIT and sublingual administration, which can be a boon for needle-phobic patients. The primary downside of SLIT is that currently it is only approved for a limited number of allergens.

SLIT Options in Canada	Grastek	Oralair	Ragwitek	Acarizax	Itulatek
Target Allergen	Grass pollen	Grass pollen	Ragweed pollen	Dust mite	Birch pollen
Administration	8 weeks prior to grass pollen season and maintain throughout the season	12 weeks prior to grass pollen season and maintain throughout the season	16 weeks prior to tree season and maintain throughout the season	Perennial	12 weeks prior to birch pollen season and maintain throughout the season
Age Indication	5-65	5-65	5-65	18-65	18-65
Strength	12-SQ Bet		2800 BAU Timothy grass	12 SQ-HDM (6 SQ-HDM *D. farinae* and 6 SQ-HDM *D. pteronyssinus*	

Table 3. Different options currently available in Canada for SLIT-tablets. Outlines timing of administration, age indication and strength of tablet.[8-12]

From the same meta-analysis that analyzed SCIT, 52 studies showed that SLIT improved short-term symptom scores, with benefit observed in those with both seasonal and perennial sensitizations.[39] Based on 52 SLIT trials, SMD medication scores demonstrated statistically significant reductions with both seasonal and perennial treatments. Similarly to the data on SCIT, both pre/co-seasonal pollen regimes and continuous SLIT treatment for pollens have been shown to be effective at reducing symptoms. However, only pre/co-seasonal treatment showed a benefit between these two approaches for reduction in medication scores. These results are summarized in **Table 4**.

	Overall (Seasonal and Perennial allergens)	Seasonal Allergens	Perennial Allergens	Pre/co-seasonal pollen regimes	Continuous treatment for pollens
SMD Symptom Scores	-0.48 (95% CI -0.61, -0.36)	−0.35 (95% CI −0.45, −0.26)	−0.81 (95% CI −1.41, −0.20)	−0.40 (95% CI −0.48, −0.32)	−0.55 (95% CI −0.98, −0.11)
SMD Medication Scores	−0.31 (95% CI −0.44, −0.18)	−0.24 (95% CI −0.38, −0.10)	−0.72 (95% CI −1.30, −0.13)	−0.30 (95% CI −0.42, −0.18)	0.00 (95% CI −0.32, 0.33) – non-significant

Table 4. SMD in symptom and medication scores for seasonal versus perennial allergens and continuous vs. pre/co-seasonal pollen regimes with SLIT.[39]

Overall, the short-term efficacy of both SLIT and SCIT combined was moderately in favour of AIT (SMD −0.53 (95% CI −0.63, −0.42)) for symptom scores and a small-to-medium effect was observed in favour of AIT for medication scores −0.38 (95% CI −0.49, −0.26).[39] The effects of SCIT and SLIT (pooled) based on the type of allergen are summarized in **Table 5**. All categories of allergen demonstrated efficacy other than mould where the effect size was quite variable for both symptom and medication scores.[39]

LONG-TERM BENEFITS

The long-term benefit of AIT, referring to the ongoing benefit after therapy discontinuation, is one of its most novel aspects. Typically, this benefit is measured at 12 and/or 24 months post-discontinuation of therapy. Studies looking at both SCIT and SLIT have shown disease-modification after 3 years of therapy with durability of response lasting as long as 12 years post-treatment (studied with grass pollen SCIT).[1-2, 5, 39-46] Specifically, these studies have found persistent reduction of symptoms, reduction in the need for medications, reduced responses to allergen challenges and improved quality of life following discontinuation of AIT. A study looking at 2 years of treatment did not confer long-term benefit hence supporting the recommendation of a minimum of three years of therapy.[47] AIT may be as close an immuno-modulatory intervention to a "cure" for moderated-to-severe allergic rhino-conjunctivitis (ARC) but has not qualified to a definite cure at this time. Regarding the issue of prevention, there is a high degree of heterogeneity among AIT prevention studies, making strong conclusions difficult to elucidate.[46]

Allergen	House dust mite (HDM)	Grass Pollen	Tree Pollen	Weed pollen	Moulds
SMD Symptom Scores	−0.73 (95% CI −1.37, −0.10)	−0.45 (95% CI −0.54, −0.36	−0.57 (95% CI −0.92, −0.21)	−0.68 (95% CI −1.06, −0.30)	−0.56 (95% CI −2.29, 1.18)
SMD Medication Scores	−0.63 (95% CI −1.12, −0.15)	−0.32 (95% CI −0.46, −0.18)	−0.40 (95% CI −0.59, −0.20)	−0.44 (95% CI −0.80, −0.09)	0.34 (95% CI −0.41, 1.09) – based on 1 study

Table 5. Different allergens studied for AIT (both SLIT and SCIT) and their respective short-term efficacy based on symptom and medication scores.[39]

A systematic review published in 2017 concluded that AIT (both SLIT and SCIT) significantly reduced the risk of onset of asthma in children older than preschool age who were the participants of the study.[45] Of note, this systematic review is limited due to the inclusion of smaller, heterogenous studies. The effect of AIT is best seen in the PAT study where grass pollen sensitized patients showed odds ratios of 2.5 and 2.7 for the prevention of asthma (95% CI 1.1-5.9) at the 5- and 10-year follow up mark.[46, 48-50] In another study, 812 children (5-12 years), with grass pollen allergic rhinoconjunctivitis and no history of asthma were included in the GAP trial, a randomized, double-blind, placebo-controlled study comprising 3 years of treatment with grass SLIT and 2 years of follow-up. Results demonstrated that asthma symptoms and asthma medication use was significantly lower in those subjects on SLIT compared with the placebo group (OR 0.66, p=0.036) but that there was no change in the time to the onset of an asthma diagnosis.[51]

Another benefit of AIT is its potential ability to inhibit future sensitization and atopic disease. A 2017 systematic review found that 10/18 studies analyzed (1,049 children and 10,057 adults) reported a reduction in the onset of new allergen sensitizations with AIT vs placebo, however the low quality evidence and high risk for bias in these studies is of concern in drawing firm conclusions.[52] Of note, dust mite immunotherapy was not shown to prevent new sensitizations.[46]

SAFETY

The side effects of SLIT and SCIT consist of both local and systemic reactions. Overall, the incidence of systemic reactions has been reported to be low at about 2% of SCIT patients and 1% of SLIT patients, with local reactions occurring much more frequently (50% of SCIT patients and 40-75% of SLIT patients).[5, 53-57] SCIT local reactions typically consist of injection site erythema, warmth and pain whereas SLIT local reactions most commonly include mouth, tongue and throat pruritis and/or swelling. A recent Canadian study found that the incidence rate of epinephrine use after SCIT to be about 1 per 1,047 injection visits with almost all of these reactions occurring within the first 30 minutes following the injection.[58] Severe systemic reactions are much less common in SLIT with some patients experiencing symptoms suggestive of GERD including abdominal discomfort or burning or ear/facial itching. Asthma exacerbations and anaphylaxis are extremely rare.[5] Hence, it is recommended that patients remain in the clinic for 30 minutes after a SCIT injection whereas only the 1st SLIT dose needs to be administered under supervision. The patient's asthma should be well-controlled, the patient should not exercise before or after the injection and patients should take an antihistamine prior to their injection. If reactions do occur, depending on their severity, the clinician and patient can decide if the immunotherapy should be continued and whether a dose reduction is warranted.

The advantages and disadvantages of SLIT and SCIT therapy are summarized in the EAACI guidelines (**Figure 1**).[5] It is imperative that primary care physicians are aware of patients who may benefit from AIT and make an appropriate referral to an allergist. The rhinoconjunctivitis quality of life questionnaire (RQLQ) consists of 28 questions in 7 domains (activity limitation, sleep problems, nasal symptoms, ocular symptoms, other non-nasal/ocular symptoms, practical problems and emotional function) which can be used prior to initiation of SLIT or SCIT and at 6-12 month intervals to track progress of patients. Having this objective measure of improvement should be considered a future standard of care in AIT management. Ongoing research in areas of peptide immunotherapy, recombinant allergens, biologics and novel adjuvants may shed light on potential future strategies that may be safer or less time consuming.[59]

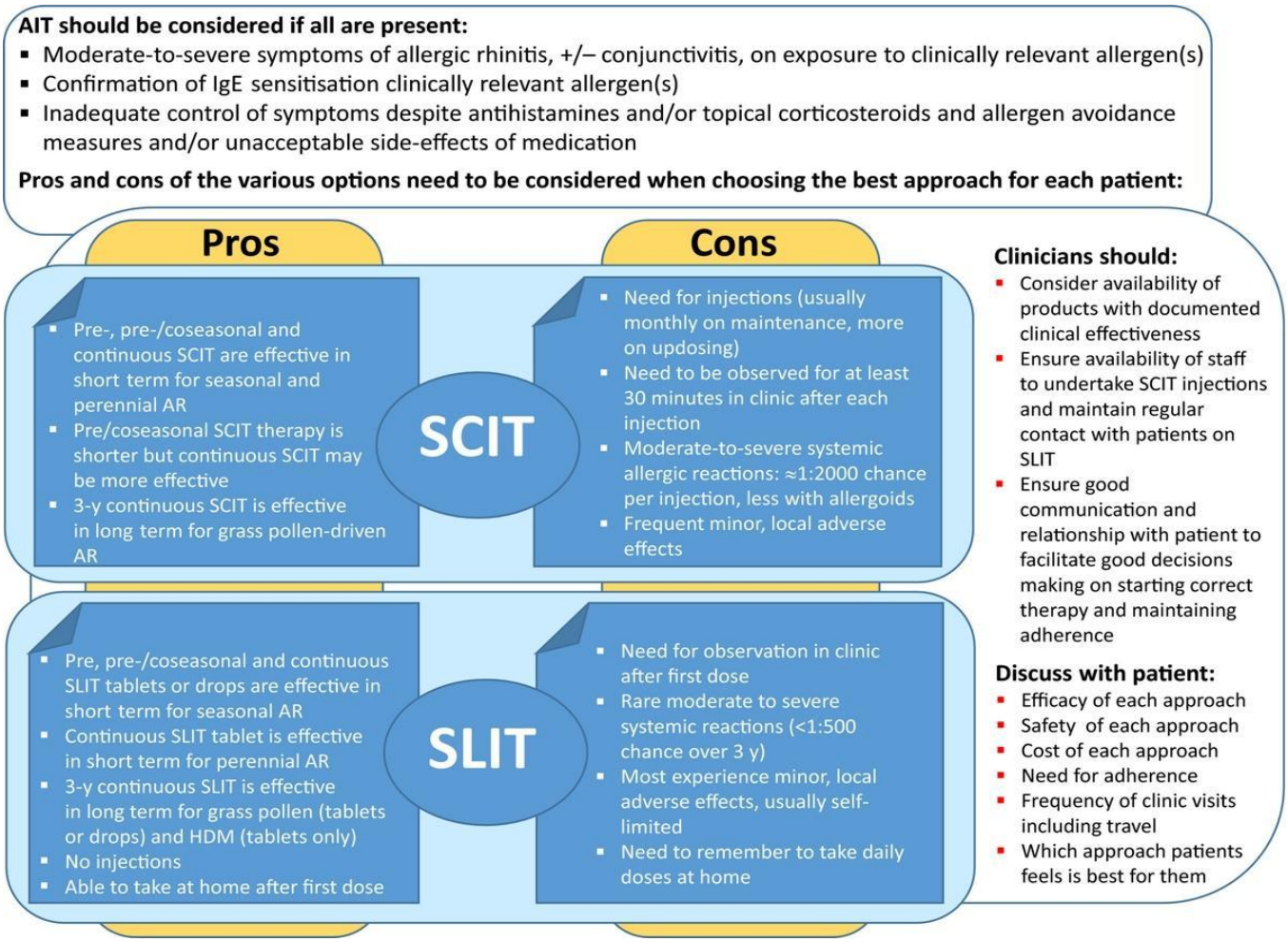

Figure 1. Advantages and disadvantages of SLIT and SCIT therapy from EAACI guidelines.

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