Immunotherapy for Asthma

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Introduction

Asthma

Asthma is a chronic inflammatory disease of the respiratory tract. Bronchospasm, airway edema and inflammation in asthma are driven by a variety of triggers and pathologic mechanisms which result in decrease in airflow, leading to respiratory symptoms and impaired quality of life (1).

Asthma represents one of the biggest global health concerns. It is thought that asthma prevalence and influence on global health will continue to increase, with anticipation of 400 million people worldwide being affected by this illness by 2025 (2). The most recent Centers for Disease Control data from 2019 estimated that approximately 8% of the population of the United States is suffering from asthma, representing 7.0% in pediatric and 8.0% in the adult population, and this prevalence has not significantly changed for the past decade (3) (4).

Several distinct asthma phenotypes have been identified based on clinical characteristics, such as age of onset, duration of disease, triggers, degree of lung function abnormalities, laboratory characteristics, and responses to therapy. Defining these phenotypes is an ongoing effort among asthma researchers, and includes single variate, multivariate, and unbiased cluster analyses (5). Ideally, understanding and defining these subgroups may lead to better application of therapies toward a precision approach. Working toward this goal, we are gaining understanding of the molecular pathophysiology, or endotype, causing disease in some of these patients (6) (7). One of the earliest recognized and described phenotypes is the allergic asthma phenotype.

Allergic asthma is most frequently defined as asthma with IgE-mediated sensitization to airborne environmental allergens, wherein asthma symptoms are triggered by exposure to those allergens. It is estimated that over 50% of adults and about 80% of children with asthma might have symptoms driven by allergen exposure (8). Patients with allergic asthma can have pan-sensitization to aeroallergens including pollens from a variety of trees, grasses, and weeds. Pro-inflammatory allergens such as mold, pet dander and dust mite may be particularly problematic among patients with asthma (9). However, sensitization is very common and does not always equate to the development of allergic symptoms, so clinical correlation between symptoms and exposures should be present with this diagnosis. Also, patients with allergic asthma can have symptoms triggered by other exposures, such as viruses and pollutants, and the airway inflammation and hyperreactivity in asthma can be persistent even with avoidance of allergens.

Allergic sensitization is an important and compelling risk factor for severity and development of asthma in both pediatric and adult patients (10). In fact, when assessing the Asthma Predictive Index in toddlers, presence of proven aeroallergen sensitization is one of the three major criteria that show risk for the development of asthma (others being atopic dermatitis and parental

asthma history) (11). Additionally, allergic asthma has been shown to have childhood onset in majority of cases; that said, even in asthma with later onset (after 12 years of age), 3 out of 4 patients have demonstrated allergic sensitization (12). Frequently, these patients also have associated symptoms of allergic rhinitis and/or atopic dermatitis (13).

Allergic asthma is by definition characterized by “type 2” inflammation, where exposure of the airways to the allergen causes degranulation of mast cells in an IgE-dependent manner. Release of histamine, prostaglandins, leukotrienes, and cytokines trigger both acute bronchoconstriction, mucus production and influx of inflammatory cells(6). Adaptive type 2 helper CD4+ T (Th2) cells are thought to drive this process through production of IL-4, IL-5 and IL-13. Therefore, in addition to production of IgE, eosinophilia is often also identified (14).

In the world of allergy, prevention of exposure is the most effective treatment. Patients with sensitization to highly prevalent or ubiquitous aeroallergens such as pollens, molds, and pet dander will have difficulty completely avoiding these exposures. To the extent that it is possible, reducing or eliminating allergic triggers from the environment has been shown to be effective for diminishing exposure in hopes of controlling symptoms (15, 16). Inhaled corticosteroids with and without bronchodilators continue to be the mainstay of treatment for the majority of patients with asthma, including for those with allergic asthma. However, advances in biologic therapy have been exceptional and biologics now play a very significant role in the treatment of poorly controlled allergic or eosinophilic asthma (17, 18). Allergen-specific immunotherapy (AIT), in the forms of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), has been used for many decades as a tool for reducing IgE-mediated sensitization and controlling symptoms of allergic disease. The use of immunotherapy for treatment of allergic asthma is the major focus of this chapter.

Immunotherapy

Allergen-specific immunotherapy represents a therapeutic approach which modulates an individual’s immune response to allergen(s) by diminishing IgE-mediated pathways while inducing immune tolerance. This treatment modality was first reported by Leonard Noon and John Freeman over a century ago, and has continued to develop and improve over time (19).

AIT is characterized by repeated administration of one or multiple allergens to which patients are sensitized, in a controlled setting, and over a period of months to years. The Food and Drug Administration has approved two forms of AIT for aeroallergen sensitization: AIT is administered subcutaneously- known as “shots”- or sublingually- through tablets or “drops”. These two modes of AIT differ not just in the route of administration, but also in efficacy, safety, and side effect profile as well as number of allergens they contain (20).

For patients receiving SCIT, a solution containing the allergen(s) a patient is sensitized to is administered as a subcutaneous injection. Initially, the SCIT dose contains very low concentrations of patient-specific allergen(s). As the course of SCIT progresses, the allergen solution becomes less dilute, therefore increasing the amount of allergen being injected which corresponds to the “build-up phase” and usually lasts about 6 months. The build-up phase is complete when the patient reaches the “maintenance dose,” a predetermined therapeutic effective dose. After the maintenance dose is reached, the time interval between administration of SCIT injections is extended to 2 and then up to 4 weeks; at which time individual is

considered to be in “maintenance phase”. At this stage, the concentration/amount of allergens injected remains unchanged. The duration of the build-up phase can be decreased by increasing frequency of SCIT injections; this is referred to as “accelerated schedule” or “cluster immunotherapy”. For majority of patients, treatment with SCIT lasts 3 to 5 years (20). Adverse reactions to SCIT commonly include injection site swelling and pruritis, and rarely can include systemic/anaphylactic reaction or death (20). As the majority of these more severe reactions occur within 30 minutes of injection, patients are recommended to be monitored in a provider’s office for that duration of time.

The FDA has approved a limited number of sublingual tablets for SLIT treatment of allergic rhinitis: Ragwitek (ALK-Abello) for ragweed allergy; Grastek (ALK-Abello) and Oralair (Greer) for Timothy grass pollen family, and Odactra (ALK-Abello) for house dust mite. Generally, patients are asked to dissolve the tablet under the tongue, not swallowing for approximately a minute. The first dose is administered under provider supervision, and subsequent doses are used daily. Seasonal allergen SLIT can be used year-round, or seasonal with pretreatment of approximately 6 weeks before the anticipated pollen season. Sublingual “drops” are not regulated, office-made mixtures of one or multiple antigens from extracts, for which target concentration of antigens is not well defined. Local effects, such as sublingual irritation or pruritus, are common but usually self-limited.

AIT targets immune processes mediated by Th2 cells and regulatory T cells (Treg) and has been known to cause a wide variety of changes on molecular and cellular levels, thus altering the natural course of allergic illnesses, including for allergic asthma (Figure 1). Several major processes have been identified as part the response to AIT (21), and the most prominent ones include:

1. Rapid desensitization of basophils and mast cells

2. Activation of regulatory T and B cells

3. B cell class switching to IgG4

4. Suppression of T lymphocytes and eosinophils (effectors of the late phase)

Practitioners should keep in mind that to this day, AIT is the only disease-modifying therapeutic modality for allergic illnesses, including allergic asthma (22, 23). Moreover, unlike inhaled corticosteroids, bronchodilators or biologics, and allergen avoidance, AIT has effects that are longer lasting, estimated to provide benefit for up to 7-12 years following discontinuation of treatment for some patients (19). Importantly, AIT has been shown to inhibit development of sensitization to new allergens and has been able to diminish evolution from allergic rhinitis to asthma in some patients (23, 24). Furthermore, as it will be discussed in detail in next sections, AIT has been proven to be an effective tool for treatment of allergic asthma, mostly in conjunction with other modalities, and is part of recommendations in a multitude of international guidelines for asthma management (25-30).

Subcutaneous Immunotherapy for Asthma

Efficacy and safety

AIT has the potential to be disease-modifying due to its immunomodulating effects, and therefore can influence severity and progression of allergic illnesses, including asthma. One should keep in mind that presence of allergen sensitization (i.e., positive allergy testing) is needed but not enough to establish diagnosis of allergic asthma. Additionally, allergen exposure is rarely the only trigger for asthma symptoms. Because of complex nature of mechanisms causing and contributing to asthma symptoms, assessing the efficacy of allergen immunotherapy in a patient with asthma can be quite challenging.

Over the many decades of studies examining the efficacy of AIT for asthma, there has been significant variability in defined outcomes, methods, and population studied. Some of the more recent efforts to comprehensively summarize this large body of data include Comparative Effectiveness Review number 196: The Role of Immunotherapy in the Treatment of Asthma (28), published in March 2018 and followed by 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group (NAEPPCC)(29), as well as a separate synthesis undertaken by Dhami et al. published in 2017, in an effort to inform the European Academy of Allergy and Clinical Immunology (EAACI) guidelines on AIT for asthma(31).

Each of these very comprehensive reviews chose different approaches when defining and prioritizing outcomes of interest. The EAACI group identified 3 primary outcomes (symptom score, medication score, combined symptom and medication score) and 7 secondary outcomes (asthma control, quality of life, exacerbations, lung function, airway hyperreactivity, cost effectiveness, safety). The NAEPPCC Expert Panel defined 3 critical outcomes (quality of life, asthma control and asthma exacerbations) and 3 important outcomes (use of quick relief medications, long-term medication use, adverse events). Note that all of the “critical” outcomes are represented in the group of “secondary” outcomes in Dhami et al.’s review and meta-analysis.

Administration of AIT is not recommended in patients with severe or poorly controlled asthma, as we will further discuss later in the chapter, due to safety concerns. Therefore, participants in SCIT clinical trials are mostly those with mild to moderate asthma.

Quality of Life

Evidence generally supports that AIT improves asthma disease-specific quality of life (QoL) measurements (32) (33, 34), even though there are some trials of single allergen SCIT in the pediatric population, that failed to confirm this (35) (36). From 3 studies that demonstrated significant improvement in QoL, two studies included only adults with mild and moderate persistent asthma, treated with house dust mite (HDM) allergen (32, 33), and the third study included population 5-18 years of age treated with SCIT for Alternaria alternata (34).

Asthma control

The NAEPPCC Expert Panel evaluated 44 studies that used symptom diaries as a measure of asthma control. The majority (26 out of 44) of studies reported improved asthma control with AIT when compared to placebo. There are no studies that presented asthma symptom control using some of the standardized questionnaires such as Asthma Control Test (ACT), Asthma Control Questionnaire (ACQ), or Pediatric-Asthma Control Test (P-ACT) scores.

Decline in quick relief medication use was reported in one study (37). Seven studies which included adult and pediatric patients evaluated effects of AIT on inhaled corticosteroid (ICS) use through variable metrics (dose, duration, rate of discontinuation of ICS) and have overall noted steroid-sparing effects of AIT (33, 36-40).

One of these studies, limited to the pediatric population, also assessed the use of other controller medications including leukotriene receptor antagonists (LTRA) and long-acting beta agonists (LABA), in addition to the use of ICS (36) and found that SCIT had sparing effects for all of the long-acting controlled medications.

Asthma exacerbations

Asthma exacerbation can broadly be defined as worsening of asthma-related respiratory symptoms requiring increased use of asthma medications, with deteriorated pulmonary function and associated morbidity and mortality risk. Given that asthma exacerbation encompasses a spectrum of symptoms, duration, severity, and required intervention, different definitions have been used in trials and therefore it may be difficult to pool data from different studies to draw a conclusion about the benefit of SCIT for asthma exacerbation prevention. Additionally, as discussed above, the majority of the studies enrolled patients with mild to moderate asthma (though some do not clearly define severity of asthma in participants), making the likelihood of exacerbations in this population overall lower. However, some of the studies were able to demonstrate statistically significant decrease in asthma exacerbations for patients on AIT (41), whereas others (40) had a low rate of exacerbation in both the SCIT and control group and failed to show protective effects of SCIT.

When treatment with a systemic corticosteroid is used to define an exacerbation of asthma, several studies in children assessed steroid-sparing effects in patients with and without SCIT treatment. Only one of these studies showed benefits of AIT use as demonstrated by diminished number of days on systemic steroids (41), whereas two others failed to demonstrate steroid-sparing effects of allergen immunotherapy (39, 42).

Airway hyperreactivity

Bronchial provocation tests have been performed in some trials in order to assess specific (allergen specific) and non-specific airway hyperreactivity (AHR) in patients on SCIT. Dhami et al. (31) reported a total of twenty trials who performed allergen-specific bronchial provocation tests which showed a significant effect on reducing AHR. Specifically, there were eight randomized controlled trials (RCTs) which proved effectiveness of SCIT on diminishing allergen specific bronchial hyperreactivity (31). This same review also identified eighteen studies evaluating effects of AIT on non-specific bronchial hyperreactivity, primarily using methacholine or histamine. Authors were able to pool data from seven studies and were able to draw the conclusion which overall favors AIT even for non-specific AHR, although to a lesser extent than when allergen specific AHR was assessed.

Lung function

Assessing lung function differed amongst different studies, not all of them consistently reporting comparison to the control groups. The majority of studies noted statistically significant but perhaps not clinically relevant improvement in peak expiratory flow (PEF) of about 5-10% and/or forced expiratory volume (FEV) of 10-15%, although not all the studies assessed for both.

These studies were performed in both pediatric and adult populations. However, when pooling data across studies, Dhami et al. noted no significant difference in PEF or FEV1. So in general, while some studies show improvement in lung function parameters, these improvement were not consistently seen across studies and may not prove to be consistently clinically relevant.

Safety

Assessment of safety was done to assess both systemic and local adverse events (AE) in both pediatric and adult populations, comparing SCIT with medication or placebo treatment. Very few studies included patients with moderate to severe asthma (43-45), in whom the frequency or severity of systemic AE may be higher, and few studies specified severity of patient's asthma.

Systemic reactions are those affecting organs separate from the site of administration, usually affecting two or more organ systems. Systemic reaction criteria were unspecified in some studies, whereas some studies were very specific and included reactions such as generalized pruritus, urticaria, eczema, unspecified rash, rhinitis, nasal congestion/obstruction, conjunctivitis, asthma, bronchospasm/wheezing, dyspnea, abdominal pain, diarrhea, and hypotension. Frequency of adverse systemic reaction was reported per injection and also as percent of patients enrolled. The highest reported rate of systemic adverse reactions was 44% in a trial for SCIT for cat from 1984, where 4 of 9 patients had a systemic AE in an adult-only trial (46). Epstein et al. recently reported surveillance data collected through the American Academy of Allergy, Asthma, and Immunology and American College of Allergy, Asthma, and Immunology, on ten years (2008-2018) of physician-reported immunotherapy experience. This latest update of yearly data collections evaluated 64.5 million injection visits, over which there were 10 reported fatalities (47). Nonfatal systemic reactions were reported in approximately 0.1% of injection visits. More severe nonfatal systemic reactions occurred in approximately 1:100,000 injections. Systemic reactions were also more frequent for those practices including higher proportions of patients with asthma, particularly severe asthma, extrapolating that the asthma diagnosis confers added risk for systemic reaction. Unfortunately, among the reported fatal reactions, asthma is the major risk factor. The potential benefit of assessing control systematically through compulsory lung function monitoring and symptom assessment prior to each injection is not known.

When specifically looking into adverse reactions in the respiratory tract, a variety of signs and symptoms has been reported, including wheezing, cough, dyspnea, bronchospasm. In total, fifteen reactions were reported across seven randomized controlled trials which enrolled overall 171 patients in the SCIT arms (28).

In summary, data evaluating the benefit of SCIT for allergic asthma generally suggest the potential for benefit, in quality of life, reduction of need for controller medications, symptom control, and airways hyperreactivity. Importantly, beneficial immunomodulating effects of SCIT are long lasting therefore potentially providing protection for years after discontinuation. Limitations to these studies include that severity of asthma is not always rigorously assessed, studies contained one or more allergens that may not be the same as used in clinical practices, and outcome definitions varied widely. However, risk for adverse reactions, especially in patients with severe and poorly controlled asthma is increased, and other factors that trigger asthma exacerbations and symptoms cannot be influenced by AIT. Asthma remains a risk factor for systemic and fatal reactions from SCIT.

<u>Current indications and recommendation for use of SCIT in patients with asthma</u>

Multiple expert organizations- including the Global Initiative for Asthma (GINA), The American Academy of Allergy, Asthma, and Immunology(AAAAI), The American College of Allergy, Asthma and Immunology(ACAAI), NAEPPCC, and EAACI all conditionally recommend use of SCIT in eligible patients with allergic asthma (26, 29, 48). All of these guidelines have clearly specified certain conditions and pre-requisites that need to be fulfilled in order for SCIT to have appropriate efficacy while maintaining the safety of patients with allergic asthma (Figure 2). SCIT should only be administered in patients with demonstrated allergen sensitization, ages 5 years and older. Both skin prick testing (SPT) and IgE serology are considered appropriate modes to demonstrate type I hypersensitivity to aeroallergens. Additionally, SCIT as part of asthma management is recommended only in patients with proven sensitization in whom the exposure to the allergen in fact triggers asthma-related (and not just other organ) symptoms, even though allergen exposure does not have to be the only mechanism causing asthma-related symptoms.

However, given that severe and poorly controlled asthma put patients at higher risk for significant and even fatal adverse reactions, and that majority of AIT research has been done in patients with mild to moderate asthma, expert groups recommend against SCIT for severe or poorly controlled asthmatics. Medication-based asthma treatment (controller inhalers, perhaps biologics) should be optimized prior to initiating SCIT. Moreover, clinicians should assess each patient's overall clinical condition and respiratory status prior to each dose of IT and decide if it is appropriate to administer IT at that specific visit (29).

Patients should receive every dose of SCIT in a controlled setting, including availability of the appropriate personnel, equipment, and medications, to monitor for and treat possible anaphylactic reactions, and they should remain under the supervision of their provider for a minimum of 30 minutes.

Sublingual Immunotherapy for Asthma

Efficacy and safety

Similarly to SCIT, sublingual immunotherapy (SLIT) has been researched in a variety of settings and outcomes in pediatric and adult population, and for patients with allergic asthma.

The groups of authors and expert panels that have compiled reviews and meta-analyses of data regarding the role of SCIT in asthma management, have also evaluated available information for safety and efficacy of SLIT in treatment of allergic asthma (28, 29, 31). The same set of outcomes were prioritized for SCIT and SLIT when defining primary vs. secondary or critical vs. important outcomes (29). Just as there is significant variability in SCIT administration protocols and dosing, SLIT literature varies by antigen, concentration, and route. The most rigorous literature surrounds the FDA-approved tablets.

As discussed previously, it is of great importance to determine the presence and significance of allergic sensitization and triggers in patients with asthma, in order to determine if allergen immunotherapy is indicated to provide better control of the disease. Specific focus has more recently been on HDM, with studies that have shown that this insect-like pest is globally the most significant indoor allergen source. In fact, in susceptible individuals, sensitization to house

dust mite develops sooner than to any other indoor allergen or polysensitization, casting a new light on potential role of this allergen in patients with atopic illnesses (49-52, 53 , 54).

Quality of Life

Multiple studies reported on asthma specific QoL as an outcome of SLIT. Some RCTs on HDM SLIT in adult patients used the tablet form (55, 56) and others used liquid formulation of SLIT (57, 58). One study that evaluated adults and adolescents who were using SLIT tablets as part of their asthma management failed to detect improvement in QoL for these patients (59). Interestingly, Pham-Thi et al. showed some improvement in QoL in pediatric patients on HDM SLIT tablets, however the patients enrolled in the study already had optimal asthma control with medications (60).

Asthma control

SLIT, as well as SCIT, is not recommended in patients with severe and poorly controlled asthma, therefore this aspect of AIT efficacy may be difficult to assess.

However, there were four studies that investigated asthma control with patients on SLIT, and out of those four studies, three demonstrated improved asthma control (55-57, 61). Of the ones who detected improvement, two were using SLIT in the tablet form. Three studies used the ACQ as a measure of asthma control. The fourth study used birch SLIT tablet and Asthma Control Test to assess asthma control (61).

Additionally, short acting beta agonist (SABA) use for patients on SLIT was evaluated more frequently than in patients on SCIT, and many studies also reported on use of inhaled corticosteroids, both of which can be used as surrogates for asthma control. SABA use was evaluated in five studies(61-63) (64) (65). Four of these studies demonstrated decrease in SABA use over 3-6 months. ICS use was assessed in several studies using HDM SLIT, in pediatric and adult populations. Different ways to assess level of ICS use were implemented, with two studies showing decrease in micrograms of ICS used (56) (57). Two other studies reported no difference in utilization of ICS between SLIT or placebo, assessed based on number of puffs (65) or micrograms (60).

Asthma exacerbations

Frequency of asthma exacerbation was assessed in several trials (59) (66) (55-57) (64). It is difficult to pool data from these studies to reach a joint conclusion given the differences in reporting, including different forms of SLIT: aqueous versus tablet. Virchow et al. (55) used HDM tablet for adults with HDM-allergy-related asthma that was not well controlled. This group showed a statistically significant improvement in a wide variety of outcomes including time to asthma exacerbation, time to first asthma exacerbations with deterioration in asthma symptoms or nocturnal awakening, time to first exacerbation with deterioration in lung function, time to first asthma exacerbation and use of SABAs, and time to first severe asthma exacerbations. Gomez et al. (64) reported statistically significant decrease in overall number of asthma exacerbations with HDM slit.

Use of systemic steroids as a surrogate measure for asthma control was assessed in one pediatric study (65) but no significant difference was noted between the placebo and HDM

group. Unfortunately, no studies evaluated for the same outcome in adult or mixed-age populations.

Airway hyperreactivity

Interestingly enough, even though allergen specific bronchial hyperreactivity was extensively researched for SCIT, only one trial in 1990 assessed this outcome for patients with allergic asthma on SLIT (67), which failed to find significant decrease in allergen specific AHR. However, there were a few trials that assessed non-specific airway hyperreactivity using a methacholine challenge, in patients on birch (61, 63), aqueous grass (68) or tablet HDM (69) SLIT. Both studies using birch SLIT discovered significant decrease in AHR in the SLIT treatment group. The HDM trial also demonstrated improvement of non-specific AHR that reflected in statistically significant increase of the methacholine dose needed to cause a 20 percent fall in FEV1 from baseline (PD20). The trial that implemented grass mix SLIT showed insignificant improvement in AHR.

Lung function

Most frequently reported lung function related outcomes for SLIT trials were PEF and FEV1. FEV1 was assessed in total of 11 studies (55, 56, 60, 61, 63) (64, 65, 68, 70-72). These studies assessed patients of pediatric and adult ages and on different types and formulations of SLIT, with some but not all studies demonstrating improvement in FEV, that ranged from 5%-20%. Specifically, one study demonstrated statistically significant improvement in FEV1 in patients on the liquid form of HDM SLIT of approximately 20% (64). All of studies evaluating pediatric patients only (65, 71, 72) showed a significant improvement in FEV1 in the SLIT group, however this was not significantly different from the placebo group, and all of these studies used aqueous SLIT.

PEF was evaluated as an outcome in five studies (57, 65, 68, 70, 71). All of these studies compared SLIT with placebo, of which three studies were using HDM and two of grass pollen SLIT. None of the studies demonstrated statistically significant improvement when compared with controls.

Safety

Assessment of safety was done in a number of studies, assessing for systemic and local adverse events in patient populations of all ages. All studies examined single-allergen therapy, with allergens including HDM, birch, and grass. Local adverse reactions consisting of itching and/or swelling of the mouth, lips, or tongue, or pharyngeal irritation are often described. Systemic reactions consistent with anaphylaxis were not reported in any of the RCTs for SLIT (55, 56, 60, 73-75), which primarily used tablet form of immunotherapy. One pediatric study specifically commented that there were no systemic allergic reactions in 86 patients treated with aqueous HDM SLIT or placebo (71).

Reported systemic events that were related to lower respiratory symptoms/bronchospasm were reported in eight RCTs including approximately 2,100 patients (55, 56, 60, 70, 73, 75-77) with risk differences between SLIT and placebo ranging from -0.089 to 0.002 (29).

<u>Current indications and recommendation for use of AIT in patients with asthma</u>

Both SCIT and SLIT seem to have a role for treatment of allergic asthma, however asthma-specific outcomes are inconsistently improved (Table 1). There are very few studies that have directly compared SCIT versus SLIT for treatment of allergic asthma, and there is currently lack of data on comparative safety and efficacy of these two AIT modalities (28). When compared SCIT, beneficial effects of SLIT for patients with allergic asthma appear somewhat less clear. The data reviewed previously shows somewhat more consistent improvement in asthma control and decrease in use of rescue medications as well as ICS in patients on SCIT comparing to SLIT, even though both modalities seem to be beneficial (31).

The review by Lin et al. (28) notes that overall, SLIT improves symptoms of asthma, decreases the use of long-term medications, improves asthma-related quality of life, and has the potential to reduce utilization of rescue medications and improve FEV1. However, NAEPPCC expert panel's latest focused updates on asthma management published in December 2020 conditionally advise against use of SLIT in patients with persistent allergic asthma, while acknowledging that use of SLIT in patients to treat the concomitant AR may contribute to reduction of asthma symptoms (29). The reason for this recommendation was because of the trivial or inconsistent benefit on asthma outcomes assessed by the panel (exacerbations, asthma control, asthma quality of life).

Specifically, for HDM, international recommendations for SLIT have incorporated the most recent research emphasizing the role of HDM sensitization in asthma and imply a specific role of SLIT for HDM in patients with mild to moderate asthma. In the 2021 GINA report, HDM SLIT is recommended as an option for step 2-4 controller therapy for patients that are 12 years or older and have "suboptimal asthma control" despite being on ICS, who also suffer from allergic rhinitis, and have proven allergic sensitization to house dust mite (26). EAACI guidelines published in 2019 recommended the tablet form of HDM-SLIT as add-on treatment to regular therapy for adults with HDM-driven allergic asthma that is well or partially-controlled(30). Both reports specify that FEV1 should be at least 70% of predicted, per the clinical trial inclusion criteria, which also defined lack of control by ACQ score of 1-1.5 and excluded those with severe asthma exacerbation within three months of HDM-SLIT initiation (55). The EAACI guidelines go further to recommend HDM-SCIT for adults and children, but only those with controlled HDM-driven allergic asthma, as an add-on therapy to decrease symptoms and medication use (30).

DISCUSSION

Evidence is unequivocal regarding immunomodulating effects of AIT in patients with proven allergic sensitization and AIT remains the only currently available disease modifying therapeutic approach in patients with atopy. Additionally, this is still the only treatment available for allergic patients that has effects lasting for many years after discontinuation and can modify development of further sensitization. Moreover, there is evidence that in subjects (especially of pediatric age) with atopy or allergic rhinitis, use of AIT has the potential to prevent development of asthma.

The two widely used forms of AIT discussed herein are subcutaneous and sublingual therapy, with extensive research done regarding both efficacy and safety of these modalities in patients with allergic asthma. However, literature is lacking in robust comprehensive head-to-head comparative evaluation of SCIT and SLIT in patients with asthma. Additionally, there is a significant inconsistency regarding the choice and definition of endpoints/outcomes amongst

existing studies of AIT in allergic asthma, making it difficult to compare and, even more so, pool data from several studies in order to reach conclusions with increased certainty and significance. Furthermore, utilization of AIT against multiple allergens, as is generally done in clinical practice with SCIT, continues to be poorly studied in this setting.

Existing data suggests, however, that AIT has a beneficial effect on allergic asthma control, including decreasing the use of short-term rescue medications as well as inhaled corticosteroids. Data on this, as well as improvement of quality of life appears more consistent for patients that are on SCIT than on SLIT. AIT, again primarily SCIT, appears to be effective in decreasing allergen specific bronchial hyper-reactivity but there are some data supporting potential benefit of SLIT on nonspecific bronchial hyperresponsiveness. The impact of both modalities of AIT on lung function is still inconclusive but they appear to improve FEV1 in some patients, and to a minimal degree. There is evidence that SCIT has some systemic steroid-sparing effects.

A pivotal role of house dust mite in pathophysiology of atopy and asthma has recently been elucidated and added significance to immunotherapy, specifically SLIT, for HDM as add on modality in patients with HDM-driven asthma that is not optimally controlled.

When assessing safety of allergen immunotherapy, it overall appears that SCIT has a higher rate of systemic adverse reactions including anaphylaxis, when compared to SLIT, but both can also cause a variety of mild local adverse reactions that significantly surpass placebo controls. Systemic reactions including anaphylaxis are more frequent in patients with asthma receiving SCIT but are overall rare.

One major limitation on the literature is that the vast majority of RCTs for SCIT and SLIT in asthma have enrolled patients with mild to moderate and well controlled asthma. For this reason, and for safety concerns, AIT is currently not recommended in patients with severe and poorly controlled asthma. Additionally, it is important to remember that implementation of AIT in patients with allergic asthma can help modify almost exclusively the response to specific allergen exposures as triggers for asthma and does not markedly influence the potential for illness related to other triggers such as exertion or infection.

Therefore, one of potential future directions of research could be an attempt to assess how AIT may have a role in management of patients with severe asthma. To this end, implementing biologic therapies against allergic pathways could be considered to assist with safe AIT introduction to patients suffering from severe allergic asthma. Also, the clinical and research community would benefit from having more universally applied definitions of asthma-related outcomes that would be consistently monitored across different studies making it easier to compare and pool data regarding safety and efficacy of AIT in asthma. Moreover, head-to-head comparisons of SCIT and SLIT for single and multiple allergen immunotherapy would further elucidate currently perceived superiority of SCIT over SLIT and help to modify guidelines. Another important addition to the decision-making process in general may be assessment of patient compliance with different modes of AIT as this can in the long-term significantly influence reaching a full therapeutic potential of immunotherapy. Given the recognized lasting immunomodulating effects of AIT, a need still exists for prospective trials that would focus on the potential impact that AIT might have on asthma control and severity during and after completion of AIT.

CONCLUSIONS

Knowledge of long lasting and immunomodulating effects of allergen immunotherapy is undeniable. Moreover, AIT has been proven to have several beneficial effects on asthma control, quality of life, and medication use in patients with allergic asthma. These benefits are notable when immunotherapy is used as an adjunct to pharmacologic treatment in carefully elected and closely monitored patients with mild to moderate persistent asthma in whom allergic sensitization has been demonstrated and allergen exposure is known to cause asthma-related symptoms.

Further research should focus on comprehensive comparative evaluation of efficacy and safety of SCIT versus SLIT, efficacy and safety in patients with severe asthma, AIT in conjunction with biologic therapy, and AIT for multiple allergens. Additionally, it may be beneficial to globally define and choose certain asthma-related outcomes and monitor them through prospective trials even after discontinuation of AIT.

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Figure 1. Anticipated immunologic changes for allergic asthma undergoing allergen-specific immunotherapy.

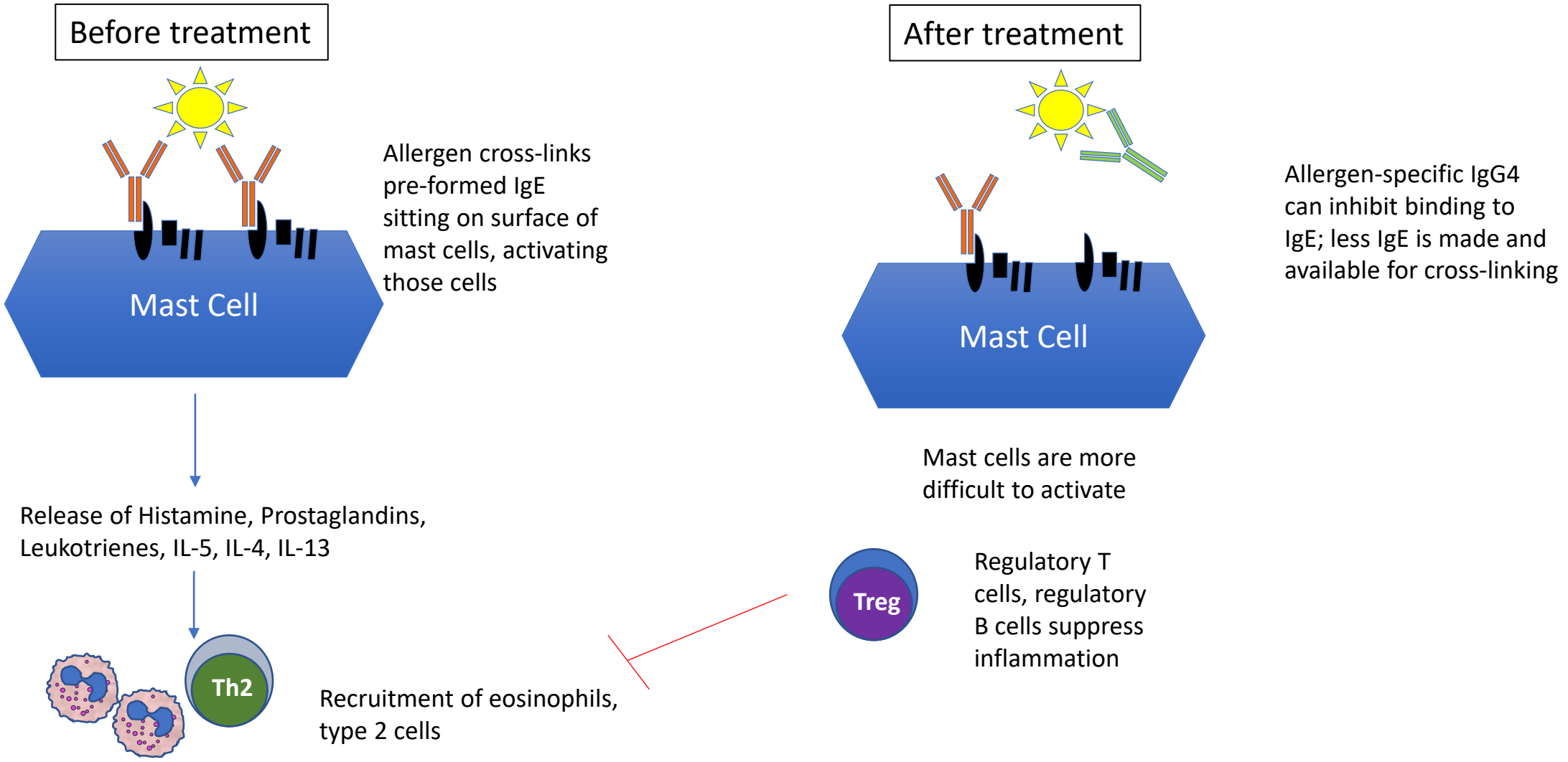

Figure 2. Decision tree for considering allergen immunotherapy for patients with asthma.

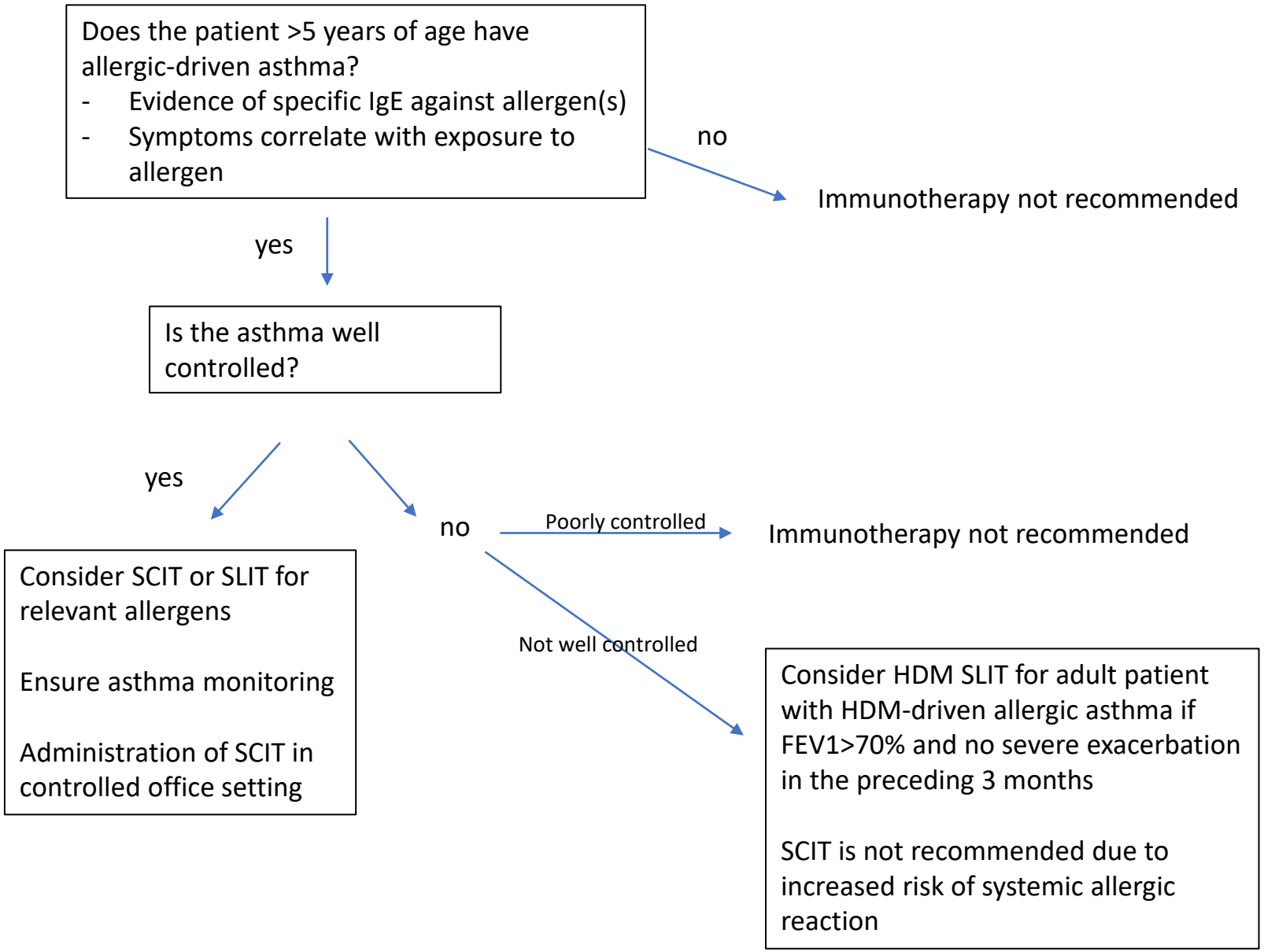

Table 1. Summary of expected benefit of sublingual and subcutaneous immunotherapy for allergic asthma.

	Efficacy			Safety
	Symptoms	Lung function	Exacerbations	
Subcutaneous (SCIT)	Improved QOL Reduced need for rescue medication Reduced need for controller/ICS therapy	Minor improvement in FEV1 or PEF Some benefit for specific and nonspecific AHR	Inconsistent benefit Did not often enroll participants with uncontrolled asthma	Major limitation for patients with asthma. Safety data lack for patients with uncontrolled or severe asthma, but current data suggest asthma is risk for systemic reactions and death
Sublingual (SLIT)	Reduced need for rescue medication Reduced need for controller/ICS therapy	Minor improvement in FEV1 Some benefit for nonspecific AHR	Inconsistent benefit Benefit for HDM tablet in adults	Rare bronchial reactions occur, rare systemic reactions

AHR Airways hyperreactivity
QOL Quality of life
SCIT Subcutaneous Immunotherapy
SLIT Sublingual Immunotherapy
FEV1 Forced expiratory volume in 1 second
ICS Inhaled corticosteroid
PEF Peak expiratory flow
HDM House dust mite