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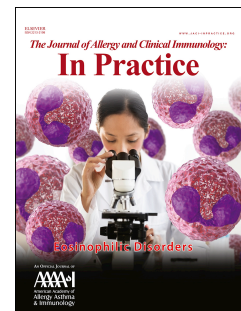
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SUBLINGUAL ALLERGEN IMMUNOTHERAPY AND ALLERGIC ASTHMA: A PRO AND CON REVIEW

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ABBREVIATIONS

AA= Allergic Asthma
AHRQ = Agency for Healthcare Research and Quality
AIT = Allergen Immunotherapy
AR = Allergic Rhinitis
ACQ = Asthma Control Questionnaire
ACT = Asthma Control Test
AQLQ = Asthma Quality of Life Questionnaire
DBPC = Double-blind placebo controlled
EBM = Evidence based medicine
EPCs = Evidence-based Practice Centers
EPR = Expert Panel Report
ICS = Inhaled corticosteroids
MA = Meta-analysis

NAEPP = National Asthma Education and Prevention Program

SLIT = Sublingual Allergen Immunotherapy

SCIT= Subcutaneous Allergen Immunotherapy

SOE = Strength of Evidence

SR = Systematic review

KEY WORDS: Asthma, sublingual, allergen immunotherapy, efficacy, safety, prevention.

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1 ABSTRACT (198 words)

2 Sublingual allergen immunotherapy (SLIT) is a therapeutic intervention used in the
3 treatment of respiratory allergies, including asthma. Multiple randomized double-
4 blind placebo controlled clinical trials have evaluated the efficacy and safety of SLIT
5 for asthma. These data provide a good platform to critically appraise the evidence to
6 evaluate the effect on SLIT in the management of asthma, for the administration of
7 SLIT by both SLIT-drops and by SLIT-tablets, from a clinical perspective. In this
8 clinical review, presented in a pro and con format, the following domains are
9 examined: i) Evidence from systematic reviews and meta-analyses, ii) Clinical
10 efficacy on asthma symptoms, asthma exacerbations and quality of life, iii) Clinical
11 efficacy on reduction of asthma controller medication, iv) Asthma severity, v) Safety
12 profile, vi) Long-term effect and prevention, vii) International guidelines and viii) Real
13 world evidence. The identified inconsistency in the data is due to wide variations and
14 differences in outcome measures, specific allergens, delivery approaches,
15 schedules, and age group. House Dust Mite (HDM) SLIT-tablet demonstrates
16 efficacy when used in the add-on management of HDM-associated allergic asthma in
17 adults. SLIT for asthma may represent an important advance in the incorporation of
18 a personalized medicine approach in patients with allergic asthma.

INTRODUCTION

Asthma, the most common chronic lower respiratory disease, is increasing in prevalence worldwide. As a complex and heterogeneous syndrome, in which genetic and environmental factors are responsible for producing symptoms, the current goals of treatment for asthma are to achieve “good asthma control” and to lower “asthma exacerbation risk”, predominantly focused on pharmacotherapy.

Although subcutaneous allergen immunotherapy (SCIT) has been globally used to treat asthma patients for many decades, its position in international guidelines and healthcare recommendations has been inconsistently recognised. This is essentially due to the fact that: i) most SCIT randomized double-blind placebo controlled (DBPC) clinical trials were not specifically designed for asthma, ii) objective measures of pulmonary function were only occasionally considered and iii) there is a confirmed risk of severe and fatal adverse events caused by SCIT in asthmatic patients, particularly those with more severe or uncontrolled asthma¹.

At least in part due to the safety profile of SCIT in some patients, sublingual allergen immunotherapy (SLIT) was proposed in 1970's as a viable alternative, more convenient and safer route to SCIT. Since then, multiple randomized DBPC clinical trials have examined the efficacy and safety of SLIT for respiratory allergic diseases, such as allergic rhinitis (AR) and allergic asthma (AA), in adults, adolescents and children using different allergens, regimens, delivery methods and dosages.

However, the role of SLIT in AA is still under consideration by many clinicians, guideline committees, and regulatory authorities due to the lack of: i) consistency amongst studies, ii) reproducibility of clinical findings, iii) consensus of the clinical outcomes to be assessed, iv) standardization of allergen dosages and regimens and v) the high cost of new SLIT formulations in some countries.

In this review we consider a variety of “pro” and “con” aspects of SLIT in the management of AA, for the administration of SLIT by both SLIT-drops and by SLIT-tablets (**Table 1**), from a clinical perspective supported by Evidence Based Medicine. Data from the assessment of major randomized DBPC clinical trials, along with the findings from systematic reviews and meta-analyses, are included. We also discuss

considerations based upon real world evidence. The reader is encouraged to evaluate all of the perspectives presented to draw individual conclusions about the various aspects of SLIT for AA.

1- SLIT AND ASTHMA: GENERAL CONSIDERATIONS WHEN EVALUATING EVIDENCE FROM SYSTEMATIC REVIEWS AND META-ANALYSES

PRO:

- Systematic reviews (SRs) and meta-analysis (MAs) provide an objective basis to evaluate the efficacy and safety of SLIT in AA. However, due to the inevitable high degrees of clinical and methodological heterogeneity of the included studies, it is not possible to have final and comprehensive answers to any specific question proposed in SRs and MAs.
- In most of the published SRs and MAs, the “overall effect” of SLIT on symptoms scores is from “moderate to large” (SMD > 0.5). This indicates that SLIT for AA is efficacious in reducing short-term symptoms scores (**Table 2**).
- We should consider evaluating only SRs and MAs with specific outcomes aiming to obtain a fair and correct answer.
- For this reason, at the present time, we might need to base our EBM criteria on both, i) previous meta-analyses and ii) individual assessment of major (superior) randomised DBPC trials for “specific” SLIT product(s) for AA.

CON:

- Not all SR/MAs are created equal, and many have methodologic or interpretative limitations that must be considered. Furthermore, the original individual papers that comprise SR/MAs often also have methodological flaws which are not overcome by SR/MA methodologies.
- In the setting of allergen immunotherapy (AIT) for asthma, many MAs do not distinguish between SCIT and SLIT, viewing AIT as a single intervention despite evidence that SCIT and SLIT differ in many aspects.
- Although the message given through MAs is generally “positive and encouraging” regarding the efficacy of SLIT in AA, we must remember that in all those MAs,

there is “considerable heterogeneity” (>75% to 100%); therefore, we need to be cautious in the interpretation and generalization of those findings (**Table 2**)².

- Additional challenges in interpreting such analyses include the following methodologic issues: inconsistent and variable outcome measures across individual studies, consideration of multiple products and allergens which may have been administered by different routes, using different formulations and dosing regimens, achieving different maintenance doses, and covering varying durations of therapy and follow up.
- Furthermore, even when SLIT is considered independent of SCIT, method of administration is often not specifically examined. SLIT when given as drops and SLIT when given as tablets should not be considered a single intervention, since these presentations likely differ in dosages, schedules, manufacturing procedures, and outcomes.
- For SRs and MAs to be truly helpful in determining the role of SLIT in the management of AA, these analyses should address very specific questions, for example: “*What is the effect of a specific SLIT-tablet regimen on AA due to HDM in adults?*”. This will narrow the heterogeneity effect and will indicate to the clinicians and regulatory agencies which product(s) should be used. Currently, such analyses are generally absent, in large part due to a paucity of SLIT studies designed to answer such focused and specific questions in well-defined populations.

2- SLIT AND ASTHMA: CLINICAL EFFICACY ON ASTHMA SYMPTOMS, ASTHMA EXACERBATIONS AND QUALITY OF LIFE

PRO:

- For clinicians, the main aim when treating a patient with asthma is to reduce his/her respiratory symptoms, firstly in short-manner, and subsequently in a long-manner. Considering the complexity of the asthma syndrome and ethical limitations, most of the current studies have evaluated only short-term reduction of asthma symptoms including cough, wheezing, shortness of breath and asthma exacerbations like any symptomatic drug.

- 117 • **HDM SLIT-Tablets:** The effect of HDM SLIT-tablet on AA has been the most

118 robustly studied and includes more than ten thousand individuals with HDM

119 respiratory allergy. All those studies are randomized DBPC trials conducted in

120 different countries and continents following the same clinical inclusion criteria and

121 using the same standardized HDM SLIT-tablet formulations.

 - 122 o The effect of a 6 SQ-HDM SLIT-tablet on asthma control as a reduction in

123 daily inhaled corticosteroids (ICS) dose from subjects' individual baseline

124 dose without deterioration in the asthma was evaluated in a randomized

125 DBPC trial with a population of 604 subjects 14 years or older with HDM mild-

126 to-moderate asthma and allergic rhinitis³. The primary analysis revealed a

127 mean difference between 6 SQ-HDM and placebo in the reduction in daily ICS

128 dose of 81 µg ($P = 0.004$). Relative mean and median reductions were 42%

129 and 50% for 6 SQ-HDM and 15% and 25% for placebo, respectively. No

130 statistically significant differences were observed for the other assessed

131 asthma parameters, reflecting the intended controlled status of the trial

132 subjects. A *post hoc* analysis on a subset of the trial's population showed that

133 subjects with a daily ICS dose of 400–800 µg and partly controlled asthma

134 (defined as an ACQ score between 1 and 1.5) at randomization experienced a

135 significantly more pronounced treatment benefit in terms of ICS reduction

136 compared to the rest of the trial population with less severe asthma. Also,

137 after 1 year of treatment with 6 SQ-HDM, the subgroup population reported

138 statistically significant improvements in asthma related quality of life (AQLQ)

139 and improved asthma control (ACQ) compared to placebo³.
 - 140 o In another randomized DBPC study conducted in 109 European trial sites,

141 834 adults with HDM allergy-related asthma not well controlled by ICS or

142 combination products, and also with HDM allergy-related rhinitis were

143 included to evaluate the effect of 6 SQ-HDM and 12 SQ-HDM SLIT-tablet vs

144 placebo for asthma exacerbations during an ICS reduction period. Efficacy

145 was assessed during the last 6 months of the trial when ICS was reduced by

146 50% for 3 months and then completely withdrawn for 3 months. The 6 SQ-

147 HDM and 12 SQ-HDM doses both significantly reduced the risk of a moderate

148 or severe asthma exacerbation compared with placebo (hazard ratio

149 [HR]:0.72 [95%CI, 0.52-0.99] for the 6 SQ-HDM group, $P = .045$, and 0.69

150 [95%CI, 0.50-0.96] for the 12 SQ-HDM group, $P = .03$)⁴.

Effect of SLIT on measures of Asthma Symptoms

- The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs)⁵, concluded that SLIT in tablet and drops/aqueous^{6, 7} forms improves asthma symptoms, as measured by validated instruments, providing a high strength of evidence (SOE) for the treatment of asthma.
- Randomized DBPC trials have shown clinical and statistically significant improvement in ACQ when used to evaluate asthma symptoms^{4, 5, 8, 9}.
- In a large clinical trial using 6SQ and 12SQ SLIT-tablet treatment vs placebo in patients with moderate to severe asthma, Virchow et al. found that 79% to 85% of participants improved in both the ACQ and the asthma quality of life questionnaire (standardized; AQLQ(S)) scores with no differences between groups, including the placebo group. However, the continuous improvement in ACQ and AQLQ(S) score adjusted for ICS use over time was seen even following ICS withdrawal, which was unexpected¹⁰.
- Another clinical study used birch allergen with a maintenance dose of 100 AU tablet 5 days per week for 3 years plus daily inhaled budesonide 400 µg daily and the Asthma Control Test (ACT) to assess asthma symptoms¹¹. The comparator group was treated with inhaled budesonide (800 µg daily, 1600 µg daily, or 400 µg inhaled budesonide plus montelukast 10 mg daily). Treatment with birch allergen for 3 years, in this study, resulted in a statistically significant improvement of ACT scores (mean post value 24 in SLIT arm, vs. 18 in other arms, $P < 0.05$).

Effect of SLIT on severe exacerbations of asthma

- For HDM SLIT-tablets, maintenance doses of 6 SQ-HDM or 12 SQ-HDM given continuously for 6 months, in comparison with placebo, showed a statistically significant improvement in all of the following outcomes with the higher dose: i) time to asthma exacerbation, ii) time to first asthma exacerbations with deterioration in asthma symptoms or nocturnal awakening, iii) time to first exacerbation with deterioration in lung function, iv) time to first asthma exacerbation and use of short acting beta-agonists (SABAs), and v) time to first severe asthma exacerbations⁴.

Effect of SLIT on asthma specific quality of life

- The impact of SLIT for AA on disease-specific quality of life using the AQLQ has been evaluated in 3 randomized DBPC trials with a total of 1,120 patients^{4, 8, 9}. Each study reported improvement in AQLQ in both the SLIT and placebo groups.
- The AHRQ review concluded that the use of SLIT may improve disease-specific quality of life with asthma, based on a body of evidence that is consistent in the direction of change, precise, direct, and with an overall low risk of bias (low SOE)⁵.

Studies of SLIT for AA in children

- Recent SR/MAs examining the role of SLIT in the treatment of allergic asthma in children have yielded inconsistent conclusions. While Kim et al. concluded that there is high strength of evidence that SLIT improves asthma symptoms¹², Rice et al. concluded there was low strength evidence that SLIT improves asthma medication use and lung function and were unable to draw conclusions on asthma symptom improvements since no studies used validated tools to capture symptoms¹³.

CON:

- Evaluating the efficacy of SLIT in asthma is highly dependent on the asthma-related outcome measures used, and the relative importance assigned to each outcome.
- Asthma guidelines often consider asthma control in two domains – short-term symptomatology (impairment) and long-term risks (often reflected by exacerbations)¹⁴.
- Clinical trials have assessed the effect of SLIT on multiple different asthma-related outcomes, with substantial variation in findings and recommendations.
- While separate SRs and MAs^{10, 12, 15-17} have all reported a “large overall” short-term benefit for SLIT-drops for symptom scores over placebo, caution is needed as there was variation in scales used, considerable inter-study heterogeneity and small population studies included. Two randomized DBPC studies including large population size and better defined outcomes have shown: i) greater but non-significantly improved asthma control¹⁸ and ii) similar incidence of asthma exacerbations between the active and placebo groups⁹. *The EAACI Guidelines on Allergen Immunotherapy: House dust mite-driven allergic asthma* concluded

that while HDM using SLIT tablets was effective in reducing exacerbations, no conclusion could be drawn for SLIT drops for HDM due to use of largely unvalidated symptom and medication scores and small sample sizes¹⁹.

- Recent efforts, such as those published in recent systematic reviews and meta-analyses, as well as those from AHRQ⁵, GINA²⁰, and the most recent NAEPP Update²¹, have drawn disparate conclusions. Such variances in interpretation and conclusions are largely due to many of the factors described above. As noted below, when evidence is indeed robust enough to lead to a positive conclusion about SLIT in asthma, it is largely limited to the setting of HDM-tablet SLIT in adults.

Effect of SLIT on measures of asthma symptoms

- As noted above, one trial showed that, despite a modest reduction in ICS dose required to maintain asthma control, one year of SLIT-tablet with HDM was not associated with significant improvements in asthma symptoms or control³.
- Despite demonstrating a reduction in asthma exacerbations, the large trial by Virchow et al did not detect a significant difference between HDM-tablet SLIT and placebo on indicators of asthma symptoms or control⁴.
- The recent AHRQ review concluded that SLIT improves asthma symptoms as measured by validated instruments (at a high strength of evidence level) based upon review of 4 RCTs (3 used HDM) involving 1193 participants⁵. However, despite evaluating the same 4 trials as the AHRQ review, NAEPP concluded that there was no difference between SLIT and placebo on the outcome of asthma control based upon inconsistent findings across the trials, and none demonstrating achievement of an established minimally important difference between SLIT and placebo²¹.

Effect of SLIT on severe exacerbations of asthma

- In a 52-week trial involving 604 participants 14 years of age and older with HDM allergy and mild-moderate asthma, house dust mite via standardized quality SLIT-tablet did not result in a reduction in asthma exacerbations³.
- In a year-long trial of HDM SLIT-tablet therapy in adults with HDM allergy-related asthma not well-controlled (ACQ at baseline of 1.0-1.5) on ICS, Virchow et al demonstrated a statistically significant reduction (HR 0.69-0.72) in risk of moderate-severe exacerbation, although this was largely due to an effect on

moderate exacerbations, with no significant effect on reduction of the more clinically relevant severe exacerbations⁴, potentially because the trial was not designed or powered for effects on severe asthma exacerbations.

- A recent randomized trial from Japan comparing HDM SLIT-tablet therapy to placebo for up to 19 months in 826 adults with mild-moderate HDM allergic asthma did not demonstrate an effect on exacerbations (as well as symptom scores, lung function or quality of life)²².
- A systematic review and meta-analysis conducted by the AHRQ found insufficient evidence on the effect of SLIT on systemic corticosteroid use (a surrogate for severe exacerbations), as well as health care utilization⁵. Using this report, the NAEPP 2020 update concluded that, based upon 3 randomized, controlled trials involving 1873 patients, the use of SLIT when compared to placebo, favored the SLIT intervention in terms of exacerbation reduction, but found no difference between SLIT and placebo in terms of systemic corticosteroid use²¹. This likely reflects reductions of moderate exacerbations that are often not managed with systemic corticosteroids.

Effect of SLIT on asthma specific quality of life

- Two trials using HDM SLIT- tablets did not demonstrate a significant effect on quality of life over placebo^{3, 4}.
- While the AHRQ review concluded that SLIT may improve disease-specific quality of life (low strength of evidence)⁵, NAEPP concluded that multiple studies showed no significant difference between SLIT and placebo on quality of life measures (high certainty of evidence)²¹.

Studies of SLIT for AA in children

- Despite reservations due to methodological and clinical heterogeneity, some systematic reviews conducted on the use of SLIT in asthmatic children demonstrated efficacy of SLIT in asthmatic children^{12, 23-25}. However, a pediatric-specific systematic review concluded that there was insufficient evidence to allow for evaluation of the effect of SLIT on asthma symptoms¹³.

3- SLIT AND ASTHMA: CLINICAL EFFICACY ON REDUCTION OF ASTHMA CONTROLLER MEDICATION

PRO:

- In the majority of MAs the “overall effect” of SLIT for AA on symptoms scores is “moderate” (SMD 0.5 - 0.8) in reducing the dose of corticosteroids necessary for the patient to control respiratory symptoms (**Table 1**).
- **HDM SLIT-Drops:** Two MAs reported significant large¹⁵ and moderate¹² decrease in rescue medication use. However, in Liao’s MA¹⁶ no reduction in medication scores was found.
- **HDM SLIT-Tablets:** In a randomized DBPC clinical trial in adults, the lowest inhaled corticosteroids (ICS) dose needed to maintain asthma control was evaluated³. A decrease in ICS dose between active and placebo at the end of trial assessment period was 81 µg, and this benefit was observed only for the highest dose (6 SQ-HDM). However, a *post-hoc* analysis showed that subjects with a daily ICS dose of 400-800 µg and partly controlled asthma at randomization experienced a significantly greater treatment benefit for the highest dose in terms of ICS dose decrease (327 µg) compared to the rest of the trial population.

CON:

- As noted above, the effect of SLIT on asthma controller (i.e. ICS) use may be dependent on ICS dose³, and thus may be limited to those receiving higher doses of ICS.
- While HDM SLIT with tablets has been demonstrated to allow for reductions in ICS dosing in most analyses in adults, such effects have not been demonstrated for SLIT in children¹³.
- It remains uncertain how long these effects last with either ongoing SLIT, or if these effects are maintained after SLIT discontinuation.

4- SLIT AND ASTHMA: ASTHMA SEVERITY**PRO:**

- Historically, most of the AIT studies have severe asthma as an “exclusion criteria”. More often, due to safety reasons, attention was mainly put on “asthma control” rather than on “asthma severity”.

- Two randomized DBPC clinical trials in adults^{4, 18} have included some GINA-defined severe asthmatics. Wang et al. found significant clinical benefits of HDM SLIT-drops in actively treated subjects with moderate, persistent asthma at baseline (401-800 µg budesonide) with better achievement of well-controlled asthma and totally controlled asthma, a higher percentage of patients with an ACQ score <0.75 and a greater mean reduction in ICS use¹⁸. Virchow et al. found that the addition of HDM SLIT-tablet to maintenance medications improved time to first moderate or severe asthma exacerbation during ICS reduction among adults with HDM allergy-related asthma not well controlled by ICS. There was an estimated absolute reduction at 6 months of 9 to 10 percentage points; the reduction was primarily due to an effect on moderate exacerbations⁴. There were no safety concerns in either study (see section 5).

CON:

- The determination of change in asthma severity (or potentially disease modification) in SLIT trials in asthma is limited for several reasons, most notably their relatively short durations (generally 1 year or less) and not using standardized measures for severity grading (such as the CASI score²⁶). Thus, when assessments of changes in severity are reported or inferred, they are generally based upon amount of controller (ICS) needed to maintain control.
- Not all trials provide data to determine the true levels of asthma severity or control, making an assessment of change in severity impossible.
- Furthermore, nearly all SLIT trials in asthma have focused on patients with mild-moderate asthma, which likely limits the ability to detect changes in severity over time.

5- SLIT AND ASTHMA: SAFETY PROFILE

PRO:

- Most MAs and randomized DBPC clinical trials on SLIT-tablets²⁷ and SLIT-drops have shown a strong and positive safety profile relative to SCIT.
- While 60% to 85% of asthmatic patients taking SLIT have local side effects, these are typically mild itching and mild swelling of the lips and floor of the mouth.

These symptoms appear within minutes or hours after taking SLIT and are usually of short duration (less than 2 weeks). They usually do not require medical treatment or dose adjustment and often self-limited and disappear during the course of treatment.

- SLIT-related systemic reactions such as urticaria, angioedema and asthma exacerbation are rare and may occur during dose escalation and maintenance phases for SLIT-drops. These reactions may be dose-dependent.
- Few clinical cases of true anaphylaxis to SLIT have been published²⁸, and no cases have been reported within the context of carefully conducted and monitored randomized controlled trials.
- No fatalities have been reported due to SLIT treatment in asthmatics or non-asthmatics.
- These events have stressed the recommendation that the first dose of SLIT-tablets should be taken in a doctor's office with an observation period of at least 30 minutes; this advice is now clearly stated in the labelling of SLIT products.
- SLIT-tablet products are under regulatory registration; therefore, any adverse event which occur in real life clinical setting should be reported.
- **Safety in Children:** In a phase 1 randomized DBPC multicenter clinical trial, 196 children received placebo, 6 SQ or 12 SQ HDM SLIT-tablet once daily for 28 days. In both active groups, the HDM SLIT-tablet doses were well tolerated. No anaphylactic reactions, systemic allergic reactions, AEs requiring epinephrine, serious AEs, or local swellings in the mouth or throat assessed as severe were reported. Local AEs were the most commonly reported treatment-emergent AEs. On day 1, the median duration of individual local AEs ranged from 1 to 43 minutes. The proportion of subjects who discontinued owing to AEs was 0%, 6.2%, and 6.2%, and who experienced treatment-related AEs was 25%, 45%, and 52% for the placebo, 6 SQ-HDM, and 12 SQ-HDM SLIT-tablet²⁹.

CON:

- Adverse reactions occur in most patients receiving SLIT, with the majority (60-85%) of asthmatic patients taking SLIT experiencing local side effects such as mild itching and mild swelling of the lips and floor of the mouth.

- Although anaphylaxis is rare, eleven cases of nonfatal anaphylaxis to SLIT have been reported²⁸.
- It remains unclear if SLIT administered for asthma in a non-clinical trial, real world setting, with the differences in adherence to therapy that typically accompany real world use, exhibits the same safety profile as that seen in carefully selected, monitored, and motivated patients participating in clinical trials.
- Real-world long-term data on adherence, as this likely impacts both efficacy and safety, are needed to fully understand the safety profile of SLIT in patients with asthma outside of clinical trials.

6- SLIT AND ASTHMA: LONG-TERM EFFECT AND PREVENTION

PRO:

- In the 5-year SQ Grass SLIT-tablet asthma prevention (GAP) study in children with grass pollen allergy, treatment with the 75,000 SQ-T grass SLIT-tablet significantly reduced the risk of experiencing asthma symptoms or using asthma medication at the end of trial (odds ratio 5 0.66, $P < .036$), during the 2-year posttreatment follow-up, and during the entire 5-year trial period³⁰.
- EAACI's SR and MA on AIT for the prevention of allergy found no conclusive evidence that AIT reduced the risk of developing a first allergic disease (primary prevention) over the short term (RR = 0.30; 95% CI: 0.04-2.09) and no randomized controlled evidence was found in relation to its longer-term effects for this outcome. There was, however, evidence of a reduced short-term risk of developing asthma in those with allergic rhinitis receiving AIT, especially in those treated with SCIT, but it is unclear whether this benefit was maintained over the longer term (RR = 0.40; 95% CI: 0.30-0.54). Subgroup analysis confirmed these findings for underage patients treated with SLIT (but not for adults), for all patients treated with SCIT, and for patients with an allergy to pollen (but not for those allergic to dust mites)³¹.
- Secondary prevention of asthma has been reported only for grass pollen³¹.

CON:

- It has long been suggested that AIT might impact the subsequent development of all forms of allergic disease. However, trials of HDM SLIT on subsequent asthma development have not been performed to date.
- The trial by Valovirta et al., which used grass tablet SLIT, employed a very appropriate and stringent definition for asthma³⁰. The primary asthma outcome, time to asthma observed at the doctor's visit and a change in FEV₁ > 12% after β_2 -agonist administration, was indeed negative (p=0.67). While there were some positive findings based upon secondary outcomes that reflected non-specific asthma-like symptoms or asthma medication use rather than the more robust outcome of asthma, these outcomes do not necessarily reflect a reduction in risk of asthma development but instead likely represent mild intermittent wheezing rather than asthma.
- The SR and MA by Kristiansen et al demonstrated no effect of SLIT on long-term asthma development³¹.

7- SLIT AND ASTHMA: INTERNATIONAL GUIDELINES

PRO:

- Based on the findings from the randomized DBPC clinical trials with 12 SQ-HDM, HDM SLIT-tablet therapy has been the only GINA-recommended SLIT approach and product since 2017³².
- GINA states that SLIT for HDM may be considered when "*HDM-induced allergic asthma not well controlled by ICS and associated with mild to severe HDM-induced AR, when the patients' asthma status is carefully evaluated before the initiation of treatment*"³².
- GINA 2018-2020 also recommends "SLIT with HDM as an add-on therapy in patients with exacerbations despite taking Step 2 therapy to decrease mild and moderate asthma exacerbations" in adults and children 12 years and older with AR and FEV₁ > 70% predicted²⁰.

CON:

- As noted above, GINA has limited their recommendation for the addition of SLIT to HDM SLIT for adults and adolescents with allergic rhinitis, HDM sensitization,

who have sub-optimally controlled asthma and $FEV_1 > 70\%$ predicted while receiving Step 3 or 4 therapy²⁰.

- The NAEPP 2020 Update, based upon the evidence summarized above, conditionally recommended *against the use of SLIT as a treatment for asthma*²¹, while acknowledging the potential desirable effects of AIT on concomitant allergic rhinitis and/or conjunctivitis.
- The most likely explanation for the discrepancy between the AHRQ and NAEPP documents is that NAEPP prespecified 3 critical outcomes (exacerbations, asthma control, and quality of life) and 3 important outcomes (quick relief medication, adverse events, and long-term medication use) in their evaluation of AIT. They concluded that the evidence for SLIT showed “trivial benefit” for the critical outcomes with moderate certainty of evidence, which heavily contributed to the final recommendation²¹. However, it should be noted that a recent editorial challenged these conclusions³³.

8- SLIT AND ASTHMA: REAL WORLD EVIDENCE

PRO:

- Recent real-life studies show that SLIT for at least 2 years results in a significant and progressive reduction in asthma treatment use during and up to 2 to 6 years after the end of a SLIT with grass tablets³⁴ and SLIT drops with birch pollen³⁵.
- Real-life studies have shown that treatment with AIT (incl. SLIT) in patients allergic to grass and birch pollen is associated with a significant reduction not only in the course of AR, but also to a reduced risk of developing asthma even in the long term (up to 6 years after stopping treatment with AIT)³⁶.
- In a large retrospective prescription database study of patients in Germany, real-world treatment of AR patients with grass pollen SLIT-tablets was associated with slower AR progression, less frequent asthma onset, and slower asthma progression³⁴.

CON:

- Challenges and limitations in the interpretation of these real-world studies are substantial and include their retrospective nature, use of databases which lack standardized clinical definitions for asthma, non-standardized treatment

regimens, and substantial risk of bias due to reliance on proxies (such as dispensing records for medication use) to infer asthma course and response³⁶.

- Furthermore, most relevant to this discussion is that all of real-world studies cited above are based upon SLIT with pollen allergens, and none with HDM, making them difficult to integrate with the RCT-derived evidence for HDM SLIT for allergic asthma.
- Real-world derived evidence specific to HDM SLIT in patients with asthma is needed to adequately assess the impact of such therapy.

CONCLUSIONS

- The evidence base that underlies a scholarly assessment of the efficacy of SLIT in the management of allergic asthma remains inconsistent.
- Many of the inconsistencies are due to wide variations and differences in outcome measures, specific allergens, delivery approaches, schedules, and age group.
- HDM SLIT-tablet demonstrates efficacy on several outcome measures when used in the add-on management of HDM-associated allergic asthma in adults.
- In contrast, SLIT with other allergens, when given by drops rather than tablets, or in children with asthma is not supported by robust levels of evidence.
- Limited data are available for relevant outcomes such as severe asthma exacerbations and disease-specific quality of life, compounded by lack of consistent use of validated symptom and medication scores. Future research in this area should use validated outcome measures and important outcomes for patients and decision makers to allow for an evidence-based determination of the potential role of SLIT as a treatment for asthma.
- It is important to consider if asthma exacerbations and improved quality of life are truly critical outcomes to assess the efficacy of SLIT (and AIT in general). We need to consider that most of the patients included in AIT clinical trials are typically not those with frequent exacerbations or uncontrolled asthma; hence, significant clinical improvement in these parameters should be assessed and real world data should be carefully analysed.
- The safety profile for SLIT is reassuring, with very few serious adverse events having been reported. It should be noted that most studies have included

511 patients with intermittent or mild-moderate asthma, precluding a determination of
512 the safety of SLIT in patients with more severe asthma. In addition, SLIT should
513 not be recommended in adults with uncontrolled asthma.

- 514 • SLIT for AA may represent an important advance in the incorporation of a
515 personalized medicine approach in patients with allergic asthma. At present, this
516 appears to be applicable in the settings of HDM-driven asthma and in patients
517 with asthma associated with allergic rhinitis. Beyond HDM, the role of SLIT in
518 patients with asthma triggered by other allergens remains controversial due to
519 heterogeneity of commercially available products and methodological limitations
520 of studies. Nevertheless, several studies and meta-analyses demonstrate
521 efficacy in various asthma outcome measures with SLIT.
- 522 • Further research is clearly needed, with studies designed specifically to
523 overcome many of the limitations of the collective literature to date. These
524 include use of validated tools to determine outcomes. Such approaches will
525 allow future SR/MA to reach more meaningful conclusions.
- 526 • Integration of EBM from randomized DBPC clinical trials and real world data
527 should be evaluated in a comprehensive manner, and new mathematical models
528 in statistics may allow this process to go one step further.

529

530 **Table 1: General comparison between SLIT-tablets vs SLIT-drops**

531

Variable	SLIT-tablets	SLIT-drops
Evidence Based Medicine	- Strong pharmaceutical clinical development - Robust quality evidence - Large phase 3 studies included - Long term and sustained effect demonstrate (1-5 years clinical trials)	- Weak pharmaceutical clinical development - Poor to moderate quality evidence - Small studies included - No available long-term and sustained effect demonstrated
Quality of SLIT products	- Good quality products are available - All SLIT-tablet products use biologically standardized and quantified allergen extracts	- Good quality products are available - Some studies used non-standardized products
Legal framework	- Regulatory procedure approval before marketed in EU and US - Under EU price and reimbursement regulation	- Commercialization approval - In EU and US there is no price regulation
Single vs multiple allergens	- Tablets mainly use single allergen source (or highly homologous) - Supporting the concept of “one product for the homologous allergen group”	- Combination of various allergens sources can be mixed - Allergen extracts from different non-homologous groups are used
Use in poly-sensitized patients	If there is not allergen cross-reactivity, there is need to use different products	- There are allergen mixtures - In same vial, various allergens can be included
Cost	Expensive	Less expensive
FDA product approval based on phase 1-3 trials	4 products (none for asthma)	None
EMA product approval based on phase 1-3 trials	4 products	None
Dose administered	- Exact dose per tablet is given - Always mono-dose	- Error range per vial or preparation - Usually, multi-dose vials
Storage condition	Room temperature	Refrigeration required

Table 2: Short-term efficacy of SLIT on Allergic Asthma

Author - Year Population	Symptoms Score SMD [95% CI]	Medication Score SMD [95% CI] I^2 (heterogeneity)
Calamita et al. 2006 Adults and children ³⁷	n=9 studies -0.38 [-0.79 to 0.03] P = 0.005 I^2 = 64%	n=6 studies -0.91 [-1.94 to 0.12] P = 0.00001 I^2 = 92%
Penagos M et al. 2008 Children ²⁴	n= 9 studies -1.14 [-2.10 to -0.18] P = 0.02 I^2 = 94.4%	n= 7 studies -1.63 [-2.83 to -0.44] P = 0.0007 I^2 = 95.4%
Liao W et al. 2015 Children ¹⁶	n=8 studies -1.20 [-2.07 to -0.33] P<0.007 I^2 = 92.3%	n=3 studies -0.52 [-1.75 to 0.71] P = 0.001 I^2 = 84.8%
Dhami S. et al. 2017 Adults and children EAACI ²³	n=6 studies -1.11 [-1.66 to -0.56] P = 0.000 I^2 = 78.5%	n = 3 studies -0.29 [-0.82 to 0.24] P = 0.028 I^2 = 72%

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