

House Dust Mite Tablets Now Officially Accepted as Treatment in GINA: What Is the Evidence and What's Next?

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Abstract

Purpose of Review This review analyzes the growing evidence regarding the standardized quality house dust mite (SQ-HDM) sublingual immunotherapy (SLIT) tablets as a valuable therapeutic option in asthma, as recently included in the treatment algorithm of the Global Initiative for Asthma (GINA) as an add-on treatment for adult patients with allergic asthma not well controlled with inhaled corticosteroids (ICS).

Recent Findings Evidence from well-designed randomized placebo-controlled clinical trials shows that the SQ-HDM SLIT tablet is effective vs. placebo in reducing both asthma symptoms and the need for ICS, as well as the risk of experiencing a moderate/severe asthma exacerbation following ICS reduction, besides having a very good safety profile and tolerability. However, some unmet needs remain that need to be resolved.

Summary The approval of the SQ-HDM SLIT tablet by regulatory authorities in Europe and the United States and its inclusion in the treatment recommendations in GINA open an opportunity window to enhance the range of management options in some patients with asthma by using an ethology-based treatment. Further studies are needed to facilitate the more complete evaluation of the therapeutic effect of this and other related products.

Introduction

Allergen immunotherapy (AIT), either subcutaneous (SCIT) or sublingual (SLIT), is a viable therapeutic strategy for some allergic diseases. It can substantially reduce

symptom scores, medication use, improve disease-related quality of life, and induce positive changes in specific immunologic markers, in addition to be

considered the only etiology-based treatment capable of modifying the natural course of allergic diseases [1]. However, the availability of well-designed, prospective, head-to-head comparative studies in AIT has been limited, and the quality of the evidence supporting its use has not been sufficiently homogenous, often suffering high variability in criteria for selection of patients, allergen extracts and dose, study duration, and outcome definitions. All these variables have made it difficult to make assumptions based on inter-study results comparison. Apart from this, some of them have been prone to severe methodological flaws [2]. In addition, SCIT has been associated with risk to potentially serious adverse effects [3•].

SLIT (either drops or tablets) has been investigated as an effective alternative to SCIT, but with a better safety profile [3•, 4, 5]. However, several issues have prevented the approval of aqueous or glycerinated liquid allergen extracts (SLIT-drops) in the United States (US) as an alternative to SCIT. One very important issue has been to determinate the effective dose, because dosing units used in European products and American products are not interchangeable [6]. Also, some SLIT drops studies performed in North America [7, 8], Asia [9], and Europe [10] could not demonstrate consistent benefit. Nevertheless, the advent of standardized quality house dust mite (SQ-HDM) SLIT tablets, supported by the evidence of high-quality clinical trials delivering prospective confirmation of AIT efficacy and safety, caused a gradual change in the regulatory status of SLIT in the US. Following the Food and Drug Administration (FDA) approval of Timo-

thy grass (Grastek®), ragweed (Ragwitek®), and 5-grass pollen (Oralair®) SLIT tablets for the treatment of grass pollen-induced allergic rhinitis in 2014, in March 2017, the FDA approved the SQ-HDM SLIT tablet for the treatment of HDM-induced allergic rhinitis in adults [11].

On the other hand, recommendations on AIT in asthma traditionally have been a highly controversial and elusive topic in some evidence-based international asthma guidelines, with most of them considering AIT as a “conditional” suggestion for selected cases of allergic asthma, and sometimes their recommendations vary substantially from one another [12•]. Since its inception in 1993 until its 2015 update, the Global Initiative for Asthma (GINA) has not only recognized the potential benefit of AIT as a non-pharmacological intervention with limited efficacy in allergic asthma (evidence level A), but also underlined its limitations, noting that the potential benefits of AIT (including SLIT) must be weighted against the risk of adverse effects and the inconvenience and cost of the prolonged use of therapy (evidence level D) [13].

But with the growing support of high-quality body of evidence favoring SLIT tablets and the consequent shift in its regulatory status, GINA, as of its 2017 update, now recommend SQ-HDM SLIT tablets it as an add-on treatment option in adult patients with allergic asthma not well controlled with inhaled corticosteroids (ICS) [14].

This review addresses the more important factors that drove this therapeutic transition, as well as product characteristics and some unmet needs about this therapeutic option in asthma.

Factors that facilitated the inclusion of SQ-HDM SLIT tablets in GINA 2017

The process for the official inclusion of SQ-HDM SLIT tablets to the treatment algorithm of adults with allergic asthma in GINA 2017 was the ultimate result of diverse factors, some of them begun several years ago with the change in the asthma treatment paradigm that considered severity as the main target of therapy, substituting it with disease control and future risk, being AIT a treatment alternative more focused on such aspects, plus also being targeted on HDM, which is recognized as the most important disease inducer of allergic asthma. Other important pharmacological and practical characteristics of SLIT tablets also contributed, but the definitive pivotal factor was the solid body of evidence resulting of a number of prospective, high-quality clinical trials assessing efficacy, safety, and tolerability, whose results were instrumental in the approval of SQ-HDM SLIT tablets by the regulatory authorities in several countries, including the US. Some of these factors are discussed below.

Control replaced severity as the cornerstone of the asthma care algorithm

One important, early factor of asthma treatment against the previous traditional algorithmic approach that favored the recent addition of SLIT tablets in GINA was to consider that disease severity should be replaced by control combined with future risk as the central factors and ultimate therapeutic targets in asthma management [15]. This transition gradually led to a paradigm shift based on assessing asthma as a non-static, dynamic entity, stressing that therapeutic decisions and further adjustments in management should be based on the level of control, regardless of asthma medication, as severity only reflects the amount of medication required to reach and maintain asthma control. Consequently, current control and future risk have been recognized as the two most important domains of asthma control, in addition to exacerbation reduction, as this lowers the future risk of impairment of lung function [16]. These are goals that AIT can effectively contribute to achieve, especially when it is based on an accurate and careful diagnosis and administered under supervision of a trained allergist. Plus, the therapeutic effect of AIT has been estimated to provide efficacy on the medium and long term, meaning that it could not only be a treatment option useful to accomplish control, but also to maintain it [17, 18•, 19••].

HDM as a therapeutic target for SLIT tablets

HDM are some of the most relevant inducers of allergic diseases worldwide, and in patients with allergic asthma sensitized to HDM, environmental exposure (mainly in the household setting) can induce persistent respiratory symptoms [20•]. *Dermatophagoides pteronyssinus* and *D. farinae*, the two most prevalent HDM species worldwide, constitutes the most clinically relevant perennial indoor allergens associated with allergic asthma [20•, 21], and this environmental exposure can play an important and well-recognized role in the onset and maintenance of the inflammatory response characteristic of asthma and other persistent concomitant or independent allergic respiratory diseases [21, 22]. Several methods for avoidance of HDM in order to reduce allergen exposure have been proposed and are widely used, but the overall quality of evidence of this strategy is rather weak or inconsistent [23–25], which represents an unmet medical need that can be solved with specific, HDM-focused treatments such as AIT. Accordingly, it is not surprising that HDM extracts as the QS-HDM SLIT tablets were studied primarily in asthma as a priority, in such a way that the body of evidence for AIT in asthma that culminated with the first official GINA recommendation on an AIT product derived from the results of clinical trials performed with HDM SLIT tablets. Nevertheless, recent evidence-weighted analyses in systematic reviews have pointed out the need to increase the quantity and to improve the quality of the evidence regarding AIT as an effective specific treatment option for HDM-related allergies including asthma [2, 21].

Pharmacological characteristics of the 12 SQ-HDM SLIT tablets

The SQ-HDM SLIT tablet has been extensively tested for the treatment of allergic rhinitis and asthma, and was initially approved in 2015 by the European Medicines Agency (EMA) for use in Europe, Australia, and Canada (ACARIZAX®, ALK, Denmark) [26] and recently by the FDA in the US (Odactra®, ALK-Abelló, US) for HDM-induced allergic rhinitis in patients 18 to 65 years of age, in whom HDM allergy has been confirmed by a positive skin test or in vitro testing for specific immunoglobulin E (IgE) to *Dermatophagoides farinae* or *D. pteronyssinus* or skin testing to licensed house dust mite allergen extracts [11]. This product, designed for self-administration and daily use, consists of a freeze-dried fast-dissolvable tablet that is held under the tongue until it is completely dissolved, containing 12 SQ-HDM units from the HDM species *D. pteronyssinus* and *D. farinae*, following a standardized production process, providing the SLIT tablet with a proportional, equivalent amount of all four major HDM allergens (Der p1, Der p2, Der f1, and Der f2) [27•]. Although traditional pharmacokinetic profile studies with SLIT are not yet available, there is no evidence suggesting that intact allergen actually enters the systemic circulation after sublingual administration, and there are no reports that SLIT affects renal or hepatic function, as reviewed on a drug profile by Canonica et al. [28••]. The acceptable dose range dose of the SQ-HDM SLIT tablet in adults was based on results of a phase I trial that compared doses from one to 32 SQ-HDM. The 16 SQ-HDM resulted the maximum tolerable dose, but with higher frequency of treatment-related adverse events, mostly local oropharyngeal reactions inherent to the sublingual route of administration (e.g., oral or tongue pruritus, mouth edema, throat irritation) [29]. Thus, 12 SQ-HDM has been adopted as a suitable dose. The optimal duration of a course of SLIT has not been clearly defined, although a minimum period of three years is commonly recommended [30]. Due to the perennial nature of HDM-induced allergic asthma, treatment with the SQ-HDM SLIT tablet may be initiated at any time of the year safely in both monosensitized and polysensitized subjects [31•].

Mechanism of action

SLIT (either drops or tablets) has been investigated as a treatment option to induce tolerance by inducing similar immunological changes related to clinical improvement compared to when administered subcutaneously, underlying several specific immunological mechanisms including (but not limited to):

- Regulation of Th2 and Treg responses and suppression of effector T cell function, mainly mediated by mucosal antigen-presenting cells) [4].
- A further immunologic tolerogenic effect mediated by the antigenic presentation through columnar mucosal cells to T lymphocytes resident in Peyer's patches in the small intestine [32].
- Stimulation of antigen-specific T helper cells to increase immunoglobulin A (IgA) production and to suppress IgE production [33].

- Increases in allergen-specific immunoglobulin G4 (IgG4), regulated by interleukin-10 [34].

Clinical efficacy in allergic asthma

The body of evidence that eventually drove the official approval through European and US regulations in favor of the SQ-HDM SLIT tablet as an add-on to ICS for the treatment of HDM-induced allergic asthma came primarily from the summarized data of three phase II and III double blind, placebo controlled, randomized clinical trials (RCT), all part of a clinical development program with different (but complementary) designs on clinical efficacy focused on relevant specific clinical end points such as reducing asthma symptoms and the need for ICS, as well as the risk of experiencing moderate/severe asthma exacerbation versus placebo following ICS reduction, which facilitated the more complete evaluation of the therapeutic effect of the SLIT tablet. The main results of these pivotal trials, summarized in Table 1, are discussed below.

Firstly, a phase II RCT evaluated the efficacy and safety of the SQ-HDM SLIT tablet in adults and adolescents with HDM-induced mild to moderate asthma [35]. The 6 SQ-HDM SLIT preparation treatment group reduced significantly

Table 1. Summary of data on efficacy from the 3 pivotal randomized controlled trials stressing SQ-HDM SLIT tablets in allergic asthma. Data from full analysis set (complementary data adapted from [28••])

Study	Primary end point	Treatment (subjects)	Estimate	Treatment effect Mean difference (95% confidence interval)	P
Mosbech H, et al. (2014) [35]	Reduction in ICS dose at end of trial (1 year)	Placebo (n = 143)	126 µg BUD	Reference	
		1 SQ-HDM (n = 146)	169 µg BUD	42.7 (– 13 to 98)	.13
		3 SQ-HDM (n = 159)	131 µg BUD	5.1 (– 50 to 60)	.85
		6 SQ-HDM (n = 156)	208 µg BUD	81.4 (27–136)	.004
Nolte H, et al. (2015) [37, 38]	Average total asthma symptom score (TASS) at the end of trial (24 weeks)	Placebo (n = 34)	1.27	Reference	
		6 SQ-HDM (n = 36)	0.59	0.7 (0.06–1.3)	.03
		12 SQ-HDM (n = 36)	0.32	0.9 (0.4–1.5)	.0007
Virchow JC, et al. (2016) [39•]	Time to first moderate/severe exacerbation from the start of the 6-month ICS reduction/withdrawal period.	Placebo (n = 257)	83 (32%) ^a	Reference	
		6 SQ-HDM (n = 237)	62 (26%) ^a	0.69 (0.49–0.96) ^b	.03
		12 SQ-HDM (n = 248)	59 (24%) ^a	0.66 (0.47–0.93) ^b	.02

ICS inhaled corticosteroid, BUD budesonide

^aNumber and proportion of participants that had an event

^bHazard ratio (95% confidence interval), active group over placebo

the dose of daily ICS to maintain asthma control from baseline (42% in the SLIT treated patients, a reduction of 462 to 258 µg, corresponding to an 81 µg difference compared to the reduction reached in those treated with placebo). Additional post hoc analysis showed that patients with a baseline medium daily ICS dose (range 400–800 µg) experienced a significantly more pronounced treatment benefit in terms of ICS reduction versus those with less severe asthma ($p = 0.001$), besides achieving better levels of disease control, and a significant improvement in asthma-related quality of life ($p = 0.04$) [36].

Another RCT, primarily designed for adult patients suffering from HDM-induced allergic rhinitis with and without asthma, observed that asthma symptoms (assessed by the average total asthma symptom score) improved significantly in those treated with a 12 SQ-HDM SLIT tablet over the placebo-treated group through a period of 24 weeks with controlled, 6-h sessions of allergenic exposure in an allergen exposure chamber [37, 38].

More recently, a phase III, three-arm trial including 834 adults with HDM-induced allergic asthma and allergic rhinitis treated with moderate to high ICS doses (400–1200 µg/day of budesonide or equivalent), randomized to receive daily treatment with placebo, 6 SQ-HDM, or 12 SQ-HDM as add-on therapy to ICS and salbutamol, in order to assess the time to suffer the first moderate or severe asthma exacerbation over a 6-month ICS 50% reduction period followed by a 3-month complete ICS withdrawal when possible [39•]. At the end of the study, there was a clinically relevant and statistically significant risk reduction of the time to first asthma exacerbation among patients treated with the SQ-HDM tablet (166 days for 6 SQ-HDM [hazard ratio 0.69], > 180 days for 12 SQ-HDM [hazard ratio 0.66] versus placebo (102 days), noting that the two SLIT modalities underpassed the pre-specified threshold for clinical risk-reduction relevance (hazard ratio < 0.70). Overall, treatment with 12 SQ-HDM was associated with a 34% risk reduction compared to placebo and an estimated absolute reduction at 6 months of 9 to 10 percentage points.

Safety and tolerability

In addition to the evidence on its clinical effectiveness, there is little doubt that one of the most important issues that delayed the approval of AIT as part of the official treatment of asthma is safety. One of the more relevant potential advantages of SLIT over SCIT (which is still not fully accepted as treatment in GINA) is its much better safety and tolerability profile. In general, a common finding in studies covering SLIT is that it is generally safe and well tolerated [3•]. Data from a recent systematic review of SLIT (both SLIT drops and tablet preparations) as a treatment of asthma pooled 3621 patients over 30 studies and noted that, although local adverse effects (risk differences ranged – 0.03 to + 0.765) were a common occurrence in both SLIT and control groups (up to 80% of patients), life-threatening reactions were uncommon, with 3 cases of anaphylaxis (2 of them polysensitized patients), and no fatalities reported [19••]. A phase I, multicenter controlled trial including 195 North American children who received 6 and 12 SQ-HDM SLIT tablet treatment for allergic rhinitis with or without asthma showed similar safety results, with treatment-related adverse events reported in 54% and 57%, respectively (vs. 43% in the placebo group), being mild throat irritation (20%), oral pruritus (17%), and lip swelling (11%) the most

commonly observed (in the 12 SQ-HDM tablet group) [40•]. The SQ-HDM SLIT tablet is contraindicated in patients with severe, unstable, or uncontrolled asthma, a history of any severe systemic reaction or severe local reaction after taking SLIT, a history of eosinophilic esophagitis, or hypersensitivity to any of the inactive ingredients (e.g., fish-derived gelatine, mannitol) [11].

Practical aspects and compliance

Despite both SCIT and SLIT have proved to be effective treatment alternatives for respiratory allergic diseases, on the practical side SLIT offers several advantages over the traditional SCIT, not only being safer, but also more comfortable, because it can be self-administered by patients or caregivers in the patient's home setting, does not require injections, and carries a much lower risk of anaphylaxis [41]. SLIT tablets can be even more convenient, as the patient initiate treatment with a full dose (this is, with no up-dosing phase), which could help to simplify the treatment schedule, besides that they are not needed to keep refrigerated, which may contribute to achieve better compliance and play positively in terms of patient preference [42].

Unmet needs and future perspective

Even though there is good quality evidence towards efficacy and safety of the SQ-HDM SLIT tablet, there are still some understudied or controversial topics that should be considered in future trials. As a recent systematic review on SLIT has highlighted, some specific aspects regarding population, intervention, and outcomes (pointed out and discussed below) need to be further studied [19••].

Some unmet needs in SLIT

Population:

- Further trials must be more uniform to include information about asthma severity/control.
- It is precise to perform more studies in pediatric populations.

Intervention

- There is a need for additional investigation in order to establish the real utility of single-allergen vs multiple-allergen AIT treatment.
- Further evidence is needed to completely establish the optimal duration of treatment with SLIT tablets.
- Efforts are required to assess AIT compliance/adherence, and the effect compliance may have on treatment.
- Follow-up studies will be instrumental to assess the long-term efficacy after the SQ-HDM SLIT tablet treatment completion.
- Further studies should be made to establish the potential utility of novel approaches such as the combination of SLIT with other forms of AIT.

Outcome measurement

- Outcome measurements throughout studies should be better standardized.

- Research in AIT to be focused also in molecular and genomic medicine alternatives.

Population

Although there is an increasing interest to investigate more about the safety and efficacy of AIT in patients with severe asthma, SQ-HDM SLIT tablets are currently labeled as contraindicated in patients with severe, unstable, or uncontrolled asthma [11]. Trials investigating SLIT tablets should be more uniform to include information about asthma severity/control, as these endpoints are not always reported in the available body of evidence. Also, it is precise to conduct more studies specifically in pediatric allergic populations, as children and adolescents usually can achieve a much better effect when starting AIT early-on, but definite indications for the use of AIT in children with asthma are still not fully clarified [43]. Recently, the use of SQ-HDM SLIT tablet was approved for adolescents with HDM-induced allergic rhinitis in some European countries [44]. Additionally, a European multicenter phase III trial (EudraCT no. 2006-004363-39; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03654976) identifier NCT03654976), currently in process of patient recruitment, will evaluate the efficacy and safety of the SQ-HDM SLIT tablet in asthmatic children and adolescents.

Intervention

Even though the clinical use and efficacy of single-allergen versus multiple-allergen AIT is a controversial point, there is a specific interest to investigate possible future options with multiple-allergen combination through SLIT tablets to polysensitized patients, as multiple-allergen SCIT treatment is frequently used in the US. Although some positive results of previous trials studying multi allergen SLIT drops has been published [45], the evidence is still inconclusive, as there are also some studies stressing that the clinical efficacy of SLIT may be actually reduced with the addition of multiple allergens [46]. Further studies are needed to completely establish the optimal duration of therapy with SLIT tablet, as this aspect has not been fully defined yet. Also, efforts are needed to assess compliance/adherence, and the effect compliance may have on asthma management.

Results from a recent systematic review suggests that 3 years of SLIT for allergic rhinitis result in clinical benefit and immunological changes consistent with allergen-specific tolerance sustained for at least 2–3 years following cessation of treatment [30]. Currently, the only HDM SLIT tablet published trial with follow-up after 1 year of active treatment showed continued control of symptoms through a second post-therapy year [47]. Further follow-up studies will be instrumental to assess the long-term efficacy after the SQ-HDM SLIT tablet treatment completion. Also, more studies are needed to fully establish if SLIT tablet treatment has the ability to alter the progression of allergic disease, as this carryover effect has been proven with other AIT modalities.

The combination of SCIT and SLIT has been proposed as a novel approach through a RCT assessing treatment with of SCIT (for induction) and SLIT drops

(for maintenance) in children with allergic asthma and rhinitis showing positive results, albeit focused mainly on short-term outcomes [48]. To date, there are no published studies assessing the concomitant or simultaneous intake of SLIT tablets with other forms of AIT, and further studies are needed to establish its real potential utility. Finally, the probable approval of another SLIT tablet product with IR (index of reactivity) standardized *D. pteronyssinus* and *D. farinae* extract (300 IR/mL), manufactured by Stallergenes Greer and currently backed by a phase II trial in Europe for use in adults with asthma, may eventually lead to perform comparative studies in the future [49].

Outcome measurement

The often very high inter-study heterogeneity has been an obstacle to analyzing pooled data across studies. There have been efforts to standardize the outcome measures, to use validated tools that allow suitable between-study data comparisons, and to establish what level of therapeutic benefit should be considered clinically meaningful in trials of immunotherapy for respiratory allergy [50]. It would be desirable that future research in AIT to be focused also in molecular and genomic medicine alternatives, to enhance allergen specificity in order to improve the efficacy and minimizing the potential systemic adverse reactions.

Conclusions

SQ-HDM SLIT tablets have proved to be effective in relevant clinical outcomes in patients with allergic asthma with proven HDM sensitivity, such as symptom improvement, requirement for ICS or the time to first asthma exacerbation upon ICS reduction, in addition to have a very good safety profile and tolerability, and its approval by European and North American regulatory authorities as well as its inclusion in the treatment algorithm in GINA open an opportunity window to enhance the range of management options in some patients with asthma by using an ethology-based treatment. However, some unmet needs in terms of population, intervention, and outcomes still need to be resolved, and further studies are needed to extend its applicability in other clinical settings in the context of the treatment of asthma and other allergic diseases, to facilitate the more complete evaluation of the therapeutic effect of this and other similar SLIT tablet preparations.

Compliance with Ethical Standards

Conflict of Interest

Jorge A. Luna-Pech, MD, PhD, declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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