

REVIEW ARTICLE

New Suggestions in Sublingual Immunotherapy for House Dust Mite-Related Allergic Diseases

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Abstract: Background: The indications for Allergen immunotherapy (AIT) in patients suffering from House Dust Mite (HDM)-related allergic diseases are presently based on incomplete data. This is essentially based on the fact that HDM allergy is difficult to evaluate in clinical trials, due to the largely variable allergen exposure and symptoms, and to the long periods of observation needed to assess the effects. In addition, at variance with pollen allergy, in HDM allergy asthma is more prevalent. However, several AIT products have been approved for HDM-induced allergic rhinitis, according to their ascertained clinical efficacy, tolerability and safety profile, particularly in the sublingual form (SLIT).

Objective: We reviewed herein the available data on AIT in patients with HDM-induced allergic diseases, with a particular attention to the new product MK-8237 HDM-SLIT tablets, concerning its efficacy and safety profile.

Method: In the recent years, several randomized placebo-controlled clinical trials have been performed in Europe, North America and Japan to evaluate the efficacy of HDM-sublingual tablets in patients with HDM-induced allergic asthma and allergic rhinitis, mainly assessing the reduction of symptoms, exacerbations and corticosteroid intake.

Results: The results of the published clinical trials were encouraging and led to the approval and commercialization of MK-8237 HDM-SLIT tablet.

Conclusion: The favorable efficacy and safety profile of MK-8237 HDM-SLIT tablets provided a consolidated therapeutic option for patients with HDM-induced allergic rhinitis and asthma.

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INTRODUCTION

The Global Initiative for Asthma (GINA) document defines asthma as a heterogeneous disease, characterized by chronic airway inflammation, the presence of variable expiratory airflow limitation and a cohort of associated respiratory symptoms (cough, shortness of breath, wheezing and chest tightness) [1]. The GINA document, as other official statements (i.e. National Asthma Education and Prevention Program - NAEPP) recommends a stepwise treatment approach that includes both the use of medications and the

control of symptoms. According to this algorithm, inhaled corticosteroids (ICS) represent the initial pharmacological option to attain and maintain asthma control, to be combined, if needed, with long-acting β_2 -agonists (LABA) plus short-acting β_2 -agonists (SABA). An important, but only recently recognized aspect of asthma is the existence of endotypes and phenotypes. So far, the Th2-high and Th2-low phenotypes are well recognized [2, 3]. The Th2-high allergic phenotype would imply the use of allergen immunotherapy (AIT).

House Dust Mites (HDM, either *Dermatophagoides pteronyssinus* and *farinae*) are a major source of inhaled allergens causing respiratory allergic diseases [4]. Sensitization to HDM can induce both allergic rhinitis (AR) and allergic asthma (AA), since the smaller allergen-carrying particles

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can reach also the more distal portions of the respiratory tree. Recent estimates show that about 42% of subjects with HDM-induced AR also suffer from AA [5].

Notwithstanding international guidelines do recognize that extrinsic allergic asthma is the most frequent form, and that HDM-induced respiratory allergy is very common in Europe, North America and several other countries, with a prevalence of immunoglobulin E (IgE) sensitization around 49% [6, 7]; allergen immunotherapy (AIT) is an underused but efficacious treatment for allergic rhinoconjunctivitis (ARC) with or without asthma. Together with omalizumab, AIT remains at present the only curative treatment acting directly on causes and not merely on symptoms of respiratory diseases. Moreover, AIT modifies the immune-response to allergens and induces immunologic tolerance [8, 9]. An interesting assumption is that children with AR/ARC receiving AIT have a decreased risk of developing concomitant asthma [10].

AIT represents an optimal additional approach, due to its complex mechanism of action [11, 12].

HDM-SLIT TABLET RATIONALE IN HDM-INDUCED ALLERGIC DISEASES

AIT modifies the immunological response towards the specific allergen, therefore it induces a tolerance to the allergen-induced symptoms [8].

From a historical point of view, subcutaneous immunotherapy (SCIT) has been the traditional form of administration of AIT for about one century. Nonetheless, the safety concerns (severe adverse events) prompted the search for more convenient and safer routes. Sublingual immunotherapy (SLIT), after its introduction, immediately appeared as a good alternative to SCIT, and its use was rapidly accepted and validated [13, 14].

The first allergen preparations for SLIT were administered by drops: patients had to keep under the tongue the solution for 1-3 minutes and then swallow. The most recent allergen preparations for SLIT are in orally-dispersable tablets. The first tablets approved for SLIT in Europe and USA were for HDM, ragweed [15] and grass pollens [15-18].

Standardized Quality (SQ) HDM SLIT-tablet (ACARI-ZAX[®], ALK, Denmark; Miticure[®], Torii, Japan; MK-8237, Merck, USA) has been recently approved by regulatory authorities in Europe for the treatment of HDM-induced AR and AA. Moreover, a HDM SLIT-tablet developed by Shionogi and Stallergenes (Actair[®]) has been registered in Japan for the treatment of HDM-induced AR. At present, SQ HDM SLIT-tablet represents the only SLIT-tablet approved as future medication for the treatment of both HDM-induced AA and HDM-induced AR.

Another sublingual preparation based on a carbamylated HDM allergoid was developed in Italy by Lofarma (Lais[®]) and approved for the treatment of HDM-induced AR. This product, commercialized since many years, is ongoing for formal marketing authorization.

MK-8237 (Merck & Co, Inc, Kenilworth, New Jersey; ALK Abellø, Hørsholm, Denmark; Torii, Tokyo, Japan) is a fast-dissolving, freeze-dried tablet composed by a 1:1 mix-

ture of *Dermatophagoides (D.) pteronyssinus* and *D. farinae*, specific for HDM – induced AR/ARC with or without asthma.

Realized through a consolidated formulation technology (Zydis[®], Catalent, UK), it has been formulated for daily, at-home sublingual administration [19, 20].

HDM-SLIT TABLETS FIRST PIONEERING APPLICATIONS IN HDM-INDUCED ALLERGIC ASTHMA

The efficacy of SLIT, as class effect, has been robustly demonstrated for AR in several meta-analyses. In many of these meta-analyses, also asthma symptoms were considered with favourable results. Nonetheless, none of the previous studies were designed having asthma outcomes as primary evaluation. More recently, the clinical efficacy of HDM-SLIT tablet could be demonstrated in several randomized, double blind, placebo-controlled clinical trials performed in Europe, and in phase III trials performed in Japan and North America [21].

Mosbech et al firstly suggested that patients with mite-induced asthma could benefit from HDM SLIT tablet preparations [22]. They enrolled subsequently 604 European patients (≥ 14 years old) with HDM – induced AR and AA, randomizing these patients in 1:1:1:1 to daily treatment with 1, 3 or 6 SQ-HDM SLIT tablets or placebo. The primary objective was to demonstrate that SLIT could reduce the total inhaled corticosteroids daily intake. They found that the 6 SQ-HDM SLIT dosage had the best correlation with the corticosteroids sparing effect producing a significant reduction in total ICS daily intake and hypothesized that patients with mild-to-moderate HDM-induced allergic asthma could significantly benefit from a SLIT supporting treatment [23].

Some years later, Virchow et al. performed another randomized, double-blind, placebo-controlled clinical trial enrolling 834 European adult patients with HDM – induced allergic asthma and/or rhinitis not fully controlled despite inhaled corticosteroids (ICS). Randomizing these patients in 2 active arms, receiving 12 SQ-HDM and 6 SQ-HDM SLIT tablets, and one control arm receiving placebo in addition to their maintenance therapy (ICS+LABA+SABA), they demonstrated that the concomitant assumption of HDM SLIT tablets can significantly extend the time to first moderate-to-severe exacerbation versus placebo, despite ICS reduction [23]. Furthermore, they demonstrated that SLIT reduced symptoms, improved asthma control and increased serum levels of allergen-specific IgG₄. Of note, a low rate of treatment-related adverse events (AEs), more prevalent in the group receiving 12 SQ-HDM SLIT tablets, especially oral itching, mouth edema and throat irritation, was reported.

DOSE- AND TIME-DEPENDENT EFFICACY OF MK-8237 ADMINISTRATION IN PATIENTS WITH HDM-INDUCED ALLERGIC RHINITIS

Several phase II and III clinical trials performed in Europe, Japan and North America assessed the tolerability and dose ranging of SQ-HDM SLIT tablets [24].

Some interesting data came from a single-site, randomized, placebo-controlled, double-blind, clinical trial conducted by Nolte and colleagues from October 2012 to August 2013 [P003 trial (ClinicalTrials.gov identifier NCT01644617)]

[25]. The aim of that study was to investigate the dose-related efficacy of MK-8237 versus placebo in terms of improvements in total nasal symptoms score (TNSS), total ocular symptoms score (TOSS) and total symptoms score (TSS) in subjects with HDM-induced AR with or without conjunctivitis and/or asthma after a 24 weeks treatment period. The investigators, based on the premise that the higher the allergen exposure, the greater is SLIT efficacy [26], performed this trial in an environmental exposure chamber (EEC) with the purpose of reducing the possible confounding factors [27]. Subjects were exposed for 6 hours in the EEC to a pre-determined airborne mixture of *D. pteronyssinus* and *D. farinae* bodies and feces. Patients were subdivided in three groups, two active arms receiving HDM SLIT tablets 6 SQ-HDM or 12 SQ-HDM daily and one control arm with subjects receiving placebo once daily for 24 weeks. At the end of the study, the authors assessed the efficacy of MK-8237 in terms of reduction in TNSS, TOSS and TSS and observed a dose- and time-dependence. Relative to placebo, at week 24, TNSS improvements were greater in the active arm receiving 12 SQ-HDM daily (48.6%), whereas subjects receiving 6 SQ-HDM daily dose had a lower average improvement (26.6%). Moreover, subjects receiving 12 SQ-HDM daily dose had a relevant improvement in TOSS and TSS relative to the control group (67.9% and 52.2% respectively). An increase in specific IgE and IgG4 at week 24 in the active arms versus placebo was seen. Furthermore, regarding the time-dependence of the effect, they noticed that all these improvements in nasal symptoms, ocular symptoms or both appeared at 8 weeks of treatment with MK-8237.

Another phase III clinical trial [MT-06 (EudraCT no. 2011-002277-38)] assessed SQ-HDM SLIT tablets efficacy for 1 year administration [28]. 992 patients with moderate-to-severe HDM-induced AR were randomized in three groups receiving 12 SQ-HDM or 6 SQ-HDM SLIT tablets or placebo, in addition to their base therapy, and analyses showed that, after a 14 weeks treatment period, all subjects receiving HDM-SLIT tablets had a relevant and durable reduction in total combined rhinitis score (TCRS) compared with the placebo group. There was a correlation between the SQ-HDM SLIT tablets dosage and the reduction in the rhinitis quality of life questionnaire with standardized activities [RQLQ(S)] and this correlation was higher for patients that had received 12 SQ-HDM SLIT tablets.

Another large phase II clinical trial [MT-02 (EudraCT no. 2006-001795-20)] valued the impact on patients with HDM-induced AR of a treatment based on HDM-SLIT tablets through the RQLQ(S). The authors found that a 1-year treatment with the 6 SQ-HDM SLIT tablets produced more pronounced differences in RQLQ(S) and TCRS compared to placebo [29].

MK-8237 TOLERABILITY PROFILE AND RELATED ADVERSE EVENTS

Since the introduction of SLIT, the burden of adverse events immediately appeared reduced as compared to the traditional subcutaneous administration. However, due to the unpredictability of adverse events, several clinical trials have been performed aiming at assessing the incidence and nature of these treatment-related AEs.

Two phase I trials assessing tolerability and dose range for treatment with SQ HDM-SLIT tablet tested doses from 1 SQ HDM-SLIT tablet to 32 SQ HDM-SLIT tablet and identified 16 SQ HDM-SLIT tablet as the maximum tolerable dose. However, since this dose determined a non-negligible number of adverse events (AE), the maximum acceptable dose was set to 12 SQ HDM-SLIT tablet [30].

Maloney and colleagues analyzed the safety and tolerability profile and occurrence and duration of local AEs of MK-8237 in children 14 to 17 years old with HDM-induced AR/C with or without asthma [31]. Patients were randomized to three arms receiving 6 SQ HDM-SLIT tablet or 12 SQ HDM-SLIT tablet or placebo daily for 28 days. The authors found that, despite the brief observation period, all local AEs were mild to moderate, occurred within 43 minutes from intake and were of short duration. The AEs included throat irritation, oral pruritus, lip swelling, tongue pruritus, oral paresthesia, oral discomfort, mouth edema, glossodynia, dysphagia, upper respiratory tract infections and ear pruritus. No systemic reaction nor anaphylaxis requiring epinephrine occurred.

The results of this phase I, multicenter, double-blinded, randomized clinical trial showed a satisfying safety profile of MK-8237 HDM SLIT tablet in children 14 to 17 years old with HDM-induced AR/C with or without asthma, and both doses were well tolerated. Generally, all AEs began in 2 weeks, lasted less than 45 minutes and also decreased over time. The authors conclude their examination stating that, since HDM-sensitive patients could have a 6-fold higher risk of developing asthma compared with pollen-sensitized patients, HDM SLIT tablets could be a potential treatment for subjects with HDM – induced allergic asthma [9].

BIODISTRIBUTION ASPECTS OF SLIT PREPARATIONS

Allergen extracts differ from traditional drugs, since they do not act on a single receptor or mediator, but rather induce a complex immunological response. For this reason, it is not possible to provide pharmacokinetic data, but the biodistribution aspects can be assessed.

Pharmacokinetics is the study of drug absorption, distribution, metabolism and excretion. An interesting pharmacokinetics study was performed by Bagnasco and colleagues, who demonstrated that, since 123I radiolabeled *Parietaria judaica* allergen (par j 1) SLIT product was kept under the tongue, no circulating radioactivity was detected, with a peak of absorption at about 90-180 minutes [32]. Moreover, plasma radioactivity of subjects treated with 123I-HDM (der p 2) peaked at 1-2 hours also in another study conducted by Bagnasco and colleagues in 2005 [33], showing that the pharmacokinetics of the sublingual way of administration is independent of the allergen involved.

On the other hand, pharmacodynamics is the study of a drug's mechanism of action and its effects on an organism. EMA guidelines stated regarding AIT products that "formal pharmacodynamic studies are not possible for allergen products" [34]. Thus, to show the effects of AIT on the immune system "IgG levels, T-cell responses and/or cytokine production

and/or modifications of the end-organ specific response” should be measured.

Once allergen tablets are put under the tongue, held for 2-3 minutes and then swallowed [35], the first pharmacodynamic detectable effects occur on dendritic cells, particularly Langherans cells, acting as antigen – presenting cells (APC) that stimulate naïve T cells to differentiate to regulatory T cells (Treg cells) (Fig. 1).

From the mucosal level, these interactions diverge to peripheral levels, involving IgG, IgA and IgE production, with Treg cells’ suppressive action on TH2 response, which plays the major role in the allergic response [36]. In fact, allergic symptoms result from the degranulation of mast cells, which is driven by IgE interactions with their high and low affinity specific receptors. Another key-event in allergic reactions is IL-4-mediated IgE production from B cells, which is driven by TH2 cells. Consequently, a shift from a TH2 response to a Treg response may inhibit these molecular mechanisms directly at their very base.

As AIT directly targets the immunological mechanisms of allergic diseases, it may be clinically effective on all symptoms of HDM-induced respiratory allergic diseases, in HDM-induced AR and HDM-induced AA as well.

Several clinical trials have considered the measurement of allergen-specific IgE, IgG4 and the levels of IgE-blocking factor (IgE-BF), which has an inhibitory activity against circulating IgEs, in subjects who had received SQ HDM-SLIT tablets. Two phase I trials showed a relevant dose-dependent increase of allergen-specific IgE levels in all subjects receiving HDM-SLIT tablets as compared to subjects receiving placebo. Moreover, these trials found also increased levels of IgE-BF after 28 days of treatment with

IgE-BF after 28 days of treatment with more than 4 SQ-HDM SLIT tablet [31].

A 24-week phase II trial assessing specific IgE and IgG4 serum levels confirmed this increment in all active groups receiving HDM-SLIT tablets during the initial 8 weeks of treatment, compared to control group, and stated that these levels were more pronounced in subjects receiving high SQ HDM-SLIT tablet doses. More importantly, significant data is that this dose-dependence reflected also in the onset and magnitude of immunological changes [26].

CONCLUSION

Since AA and AR frequently coexist in patients with HDM sensitization and since these patients require a 360 degrees treatment, we conclude our literature revision stating that, as assessed by other authors before, further investigations are needed to apply this treatment to a larger number of patients.

According to the “united airways disease” theory, which underlines the reciprocal link between the upper and the lower respiratory tracts, treating a single disease does not meet the goal [37]. It is necessary to realize a full therapeutic program which includes both AA’s and AR’s therapies because treating only AR or AA does not permit to join an optimal condition. Treating HDM-induced AR permits a better treatment of concomitant HDM-induced AA and vice versa the treatment of AA permits a better treatment of concomitant AR.

Another potentially interesting application of MK-8237 SQ-HDM SLIT tablet could be atopic dermatitis (AD), which is a chronic, relapsing-remitting, eczematous skin

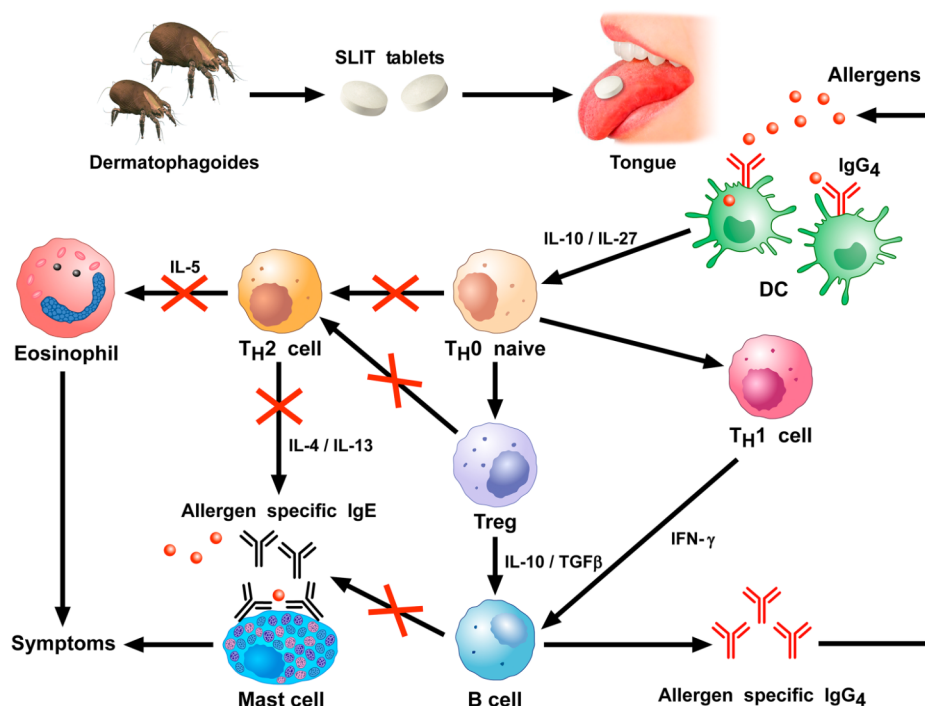


Fig. (1). HDM SLIT tablets modulate the immune system promoting the production of allergen specific antibodies with the purpose of reducing symptoms in case of new expositions to HDM.

disease that is typically associated with HDM or food allergens sensitization. Although several trials obtained favorable results, it is still controversial whether AIT application in patients with AD may bring benefits and this, at present, does not allow a formal recommendation [38-40].

The aim of this review was to analyze the contribution made by MK-8237 HDM-SLIT tablets to this goal, since its efficacy in acting directly on the pathogenetic mechanisms of both the atopic diseases is under examination.

Since the presence of concomitant AA and AR in subjects with HDM sensitization is not far uncommon, an ideal treatment should include AIT. However, despite guidelines have gathered this therapeutic approach to the pivotal strategies, this combination therapy is still underused and needs to be fully highlighted to obtain a comprehensive therapeutic management plan for these patients.

The use of MK-8237 HDM-SLIT tablet could be an example of the application of the Personalized or Precision Medicine approach in allergic diseases [41] to underline the importance of deepening our knowledge on the pathophysiological bases of HDM-induced AA and AR and select allergic patients that would benefit most from this treatment first and secondarily to guarantee the most convenient allocation of economic resources in this period of economic restrictions.

At present, few trials have investigated HDM-SLIT tablet contribution in reducing asthmatic symptoms, risk of severe exacerbations and ICS intake.

The sublingual route permits a useful at-home self-administration, once the initial treatment has been administered under medical supervision.

Eventually, the approbation by regulatory authorities of the SQ HDM-SLIT tablet for the treatment of HDM-induced allergic asthma underlines the fact that SLIT is a novel treatment option for patients with HDM-induced allergic asthma, for whom AIT has not previously been recommended.

EXPERT COMMENTARY

Currently, AIT inclusion in asthma management is left to the choice of specialists and even international guidelines do not give much space to allergen specific immunotherapy. The optimization of asthma therapy, including HDM SLIT tablets, should definitely be considered in selected patients with HDM-induced, mild-to-moderate, allergic asthma with the aim of improving asthma control, reducing exacerbation rates and corticosteroids intake.

FIVE-YEAR VIEW

Specific immunotherapy hopefully would be included as a supporting treatment in asthma guidelines within next years. This would help to increase asthma control in subjects with HDM-induced AA and concomitant AR with/without conjunctivitis. The aim of this supporting treatment with specific immunotherapy would be to reduce asthma exacerbations, increase asthma control and reduce corticosteroids intake.

KEY ISSUES 8-10 bullet points summarizing the review.

- International guidelines at present do not give much evidence to AIT utilization in asthma therapy.
- Selected HDM-sensitized patients could benefit from a supporting treatment based on HDM SLIT tablets.
- Initially the subcutaneous and recently the sublingual routes have been proposed.
- MK-8237 HDM SLIT tablets could provide benefits to selected HDM-sensitized patients with mild-to-moderate asthma.
- Several clinical trials showed significant positive results in subjects treated with HDM SLIT tablets in terms of reduction of exacerbation rates and steroids intake.
- No severe HDM SLIT tablets-related adverse events have been reported.
- New possible therapeutic approach with HDM SLIT in atopic dermatitis (AD).
- SLIT could be considered as a personalized medicine approach in the therapy of allergic people.

CONFLICT OF INTEREST

GWC has been member of advisory board, speaker, scientific meeting for GSK, Teva, Sanofi, Roche, Novartis, Astra Zeneca. GP was consultant/speaker for ALK-Abellø, AstraZeneca, Lofarma, Novartis, Stallergenes-Greer.

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AUTHORSHIP

All the signed authors have equally contributed in the preparation of this review, and have approved its final version and submission.

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