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Drug Evaluation:

MK-8237 House Dust Mite Vaccine for treating allergic rhinitis, asthma and atopic dermatitis

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ABSTRACT

Introduction. Since its introduction in clinical practice one century ago for the treatment of respiratory allergic diseases, allergen-specific immunotherapy (AIT) has exhibited a relevant clinical efficacy that was subsequently confirmed in controlled trials. Thus, AIT has been accepted worldwide, as testified by guidelines and international documents. AIT is considered pivotal in the management of allergic rhinitis with or without conjunctivitis and with or without asthma. These conditions, in addition to hymenoptera venom allergy, currently are the accepted indications. The use of AIT in house-dust mite allergy still remains debated, especially due to the methodological problems in assessing this form of respiratory allergy. The more recent experimental data on MK-8237 sublingual tablets provided evidence that AIT, in the sublingual form, is effective in dust mite allergy.

Areas covered. At present, the evidence of the efficacy of AIT in conditions other than respiratory allergy are not conclusive, but encouraging results have been obtained in food allergy and atopic dermatitis. Herein, the authors discuss the data for these indications.

Expert opinion. Not all patients respond to AIT in the same way. Accordingly, AIT represents a promising path to precision medicine and hopefully will be able to reduce this burden of non-responding patients.

KEY WORDS: allergic rhinitis; allergic asthma; atopic dermatitis; House Dust Mite, MK-8237; sublingual immunotherapy

1. INTRODUCTION

Allergen Immunotherapy (AIT), since its empirical introduction one century ago, rapidly became a cornerstone in the therapeutic management of allergic diseases, initially for patients with pollen-induced symptoms (hayfever) and later on for house dust mite (HDM)-related diseases. The IgE mediated nature of rhinoconjunctivitis and asthma was ascertained during the 1960ties, and in parallel the first randomized controlled trials were performed. Afterwards, a large number of clinical studies were carried out, consistently showing that AIT was able to reduce the severity of symptoms and the need for rescue medications under allergen exposure. AIT was administered only via the subcutaneous route (SCIT) until 1986, when the possible risk of severe adverse events was finally acknowledged. This led to the development of safer routes of administration, and the sublingual one (SLIT) achieved a scientific credibility [1]. Nowadays, SLIT is considered a viable and equivalent alternative to SCIT in all guidelines. Nonetheless, some discrepancies remain between the results obtained with pollen allergens and HDM.

HDM are ubiquitous and, among inhalant allergens, sensitization to HDM has been identified as one of the most prevalent sensitizations, with a global prevalence of 1-2%. [2-4]

At present, it is well-known that HDM sensitization can involve both upper and lower respiratory airways, provoking either allergic rhinoconjunctivitis (AR) and allergic asthma (AA). In fact, according to the Unified Airway Disease theory proposed by several Authors, the upper and lower respiratory tracts should be considered as a continuous in terms of physiology and pathogenetic mechanisms involved in respiratory diseases. [5]. HDM sensitization is most commonly associated to the development of AA, [6], but its prevalence is high also among rhinitic subjects. In fact, prevalence studies on allergen sensitization suggest that almost all patients with HDM-induced AA suffer also from AR and almost 50% of patients with HDM-induced AR also have AA. [7, 8]

2. THE MK-8237 HDM SUBLINGUAL TABLETS

The first empirical use of AIT dates back to 1911, with the pioneeristic studies by Noon [9] in hayfever and the first randomized, placebo-controlled clinical trial was performed by Frankland in 1954. [10]

Subcutaneous immunotherapy (SCIT) was the first route of AIT administration proposed for treating AR, but safety concerns emerged soon, with relevant SCIT-related systemic adverse events, and some fatalities [11]. The introduction of sublingual formulations in 1986 (SLIT) brought an important reduction of related serious systemic adverse events, this granting a safer and more convenient route of administration. SLIT was rapidly accepted and validated. [12-14]. The earliest SLIT preparations were in drops, to be kept under the tongue for 1-3 minutes and then swallowed. The most recent SLIT formulations are in sublingual dissolving tablets [15]. (FIGURE 1 [1]) MK-8237 (Merck & Co, Inc, Kenilworth, New Jersey; ALK Abellø, Hørsholm, Denmark; Torii, Tokyo, Japan) HDM-SLIT tablets are the recently developed freeze-dried, fast-dissolving sublingual tablets containing a 1:1 mixture of *Dermatophagoides pteronyssinus* and *farinae* major allergens, from HDM feces and bodies. MK-8237 SLIT tablets have been approved in 11 European countries for the treatment of HDM-induced AR with or without AA. The formulation of tablets relies on a validated technology (Zydis®, Catalent, UK). The first dose is given under direct medical supervision, whereas the continuation of the SLIT course is self-managed by patients. [16, 17].

3. MK-8237 HDM SLIT TABLET IN ALLERGIC RHINITIS (TABLE 1)

Several clinical trials assessed the efficacy and tolerability of grass pollen SLIT tablets in allergic rhinitis with favorable results. [18-21]. These were then followed by HDM and ragweed SLIT preparations.

Several randomized, double blind, placebo-controlled clinical trials performed in Europe, Japan and North America demonstrated the efficacy of HDM-SLIT tablets. [22]

Two phase I trials assessed the dose ranging and tolerability of Standardized Quality (SQ) HDM SLIT tablets and identified a maximum tolerated dose of 16 SQ-HDM, and an optimal maintenance dose of 12 SQ-HDM. [23].

Three randomized, double-blind, placebo-controlled clinical trials evaluated the efficacy of HDM SLIT tablets.

In MT-02 (EudraCT no. 2006–001795-20), a large phase II trial, impact of HDM SLIT tablets on AR was evaluated using a combined symptoms-medications score (total combined rhinitis score, TCRS). [24] A 6 SQ HDM SLIT tablet given for 1 year produced a statistically significant reduction of TCRS of 28.8% compared to placebo and an improvement in quality of life, and sleep quality in particular, assessed by the rhinitis quality of life questionnaire with standardized activities [RQLQ(S)] Adverse events were noted in up to 63% patients on active SLIT treatment and up to 57% patients receiving placebo and the most common adverse events reported were oral pruritus in the active arms and upper respiratory tract infections in the control arms.[24].

Nolte et al performed the P003 trial (ClinicalTrials.gov identifier NCT01644617), a single-site, randomized, double-blind, placebo-controlled clinical trial between October 2012 and August 2013 to assess whether MK-8237 HDM SLIT tablets improve total nasal symptoms score (TNSS), total ocular symptoms score (TOSS) and total symptoms score (TSS) in subjects with HDM-induced AR and/or asthma in a 24-weeks treatment period. [25] The evaluation was carried out by an environmental exposure chamber (EEC), with challenge periods of 6 hours, assessing symptoms every 15 minutes. [26] Subjects were randomized in two active arms receiving 6 SQ-HDM SLIT tablets or 12 SQ-HDM SLIT tablets and one control arm receiving placebo once daily for 24 weeks. The treatment with MK-8237 achieved statistically significant reductions in TNSS, TOSS and TSS in both active arms, with a dose- and time-dependence. Subjects receiving 12 SQ MK-8237 HDM SLIT tablets had a higher improvement in TNSS, TOSS and TSS compared to subjects receiving 6 SQ MK-8237 HDM SLIT tablets or placebo. Moreover, allergen-specific IgG4 increased in both active groups compared to the control group. This trial concluded for the clinical efficacy and the

faster onset of action of the 12 SQ MK-8237 HDM SLIT tablets, compared to the 6 SQ HDM dose. The majority of treatment-related adverse events were mouth and throat transient local allergic reactions.

MT-06 (EudraCT no. 2011–002277-38), a phase III trial on SQ HDM SLIT tablets clinical efficacy, evaluated TCRS in a treatment period of 1 year. [27] 992 adults with moderate-to-severe HDM-induced AR were randomized to receive, in addition to their allergy therapy, placebo or 6 SQ HDM SLIT tablets or 12 SQ HDM SLIT tablets. Both active groups showed significant TCRS differences after 14 weeks of treatment compared with the placebo group and these differences were maintained throughout the whole study. Furthermore, compared with placebo, 12 SQ HDM treatment for 1 year produced lower RQLQ(S) scores, whereas 6 SQ HDM did not produce statistically significant results. Thus, 12 SQ HDM treatment resulted clinically efficacious and relevant to patients with HDM-induced AR. Overall, HDM SLIT tablets were well-tolerated and the majority of adverse events were transient, mild and local allergic reactions including oral pruritus, throat irritation and mouth edema, which occurred within the first days of treatment and subsided in few days-weeks of continue treatment [27].

4. MK-8237 HDM SLIT TABLET IN ALLERGIC ASTHMA (TABLE 2)

The most recent Global Initiative for Asthma (GINA) guidelines provide an updated definition of asthma but attribute only a marginal role to AIT in the treatment of AA. [28]. GINA guidelines recommend a stepwise therapeutic approach to asthma control, using an algorithm based on inhaled corticosteroids (ICS) plus long-acting β_2 -agonists (LABA) or other controller medications to gain and maintain asthma control, adding short-acting β_2 -agonists (SABA) to face breakthrough symptoms. According to GINA, AIT prescription should be carefully evaluated by specialists in patients clearly suffering from mild-to-moderate pollen and HDM - induced allergic symptoms, highlighting the need of selecting patients with AA who may benefit. Albeit AIT has

shown a relevant efficacy in selected patients, GINA guidelines give AIT a low level of evidence (evidence D). According to literature reviews, only severe uncontrolled asthma remains an absolute contraindication to AIT [29].

Some years ago Mosbech and colleagues speculated if patients with HDM-related allergic asthma could benefit from an AIT supporting treatment. [30] They enrolled 604 subjects (≥ 14 years old) with HDM-induced allergic rhinitis and mild-to-moderate asthma. Randomizing these subjects in 1:1:1:1 to double-blind daily treatment with active doses (1, 3, or 6 SQ - HDM) or placebo, they wanted to prove SLIT efficacy in reducing patients' corticosteroids dose-dependence. They found that this steroid-sparing effect was dose-dependent, higher in subjects receiving 6 SQ HDM-SLIT tablet versus subjects receiving lower doses or placebo, and that mild-to-moderate HDM-sensitized asthmatic patients could significantly benefit from specific immunotherapy.

Virchow et al. performed a multicenter, randomized, double-blind, placebo-controlled clinical trial, involving 834 adult patients with HDM-induced allergic asthma and/or rhinitis not fully controlled despite inhaled corticosteroids (ICS). Patients were randomized in three arms receiving 6 SQ-HDM, 12 SQ-HDM SLIT tablets or placebo, respectively, in addition to their standard asthma therapy with ICS and SABA. All these subjects underwent ICS reduction and the primary outcome was assessing time to first moderate-to-severe exacerbation. Secondary outcomes were asthma symptoms control, specific IgG₄ concentration, asthma-related quality of life (QoL) and occurrence of adverse events. The main result was that both arms treated with HDM SLIT tablets had a significant reduction in terms of risk of moderate-to-severe asthmatic exacerbation compared with placebo. Furthermore, both active arms showed a reduced risk of breakthrough symptoms, a better asthma control and an increased plasma levels of allergen-specific IgG₄. On the other hand, no statistically significant differences in QoL were found between subjects receiving HDM-SLIT tablets and those receiving placebo. The most common treatment-related adverse events were: oral itching (13% in the 6 SQ-HDM, 20% in the 12 SQ-HDM arm and 3% in the placebo group), followed by mouth edema and throat irritation. [31]. These large studies confirmed the beneficial role of AIT in mild-to-moderate

HDM-induced asthmatic patients, not fully controlled with ICS, with important achievements, such as the corticosteroid-sparing effect and the increased time elapsed to first asthma exacerbation. The further steps in research include the demonstration of a persisting effect in the long periods (years) and, possibly the carry-over effect after discontinuation of treatment.

5. FUTURE PERSPECTIVES FOR HDM AIT IN ATOPIC DERMATITIS

Atopic Dermatitis (AD) is one of the most common chronic eczematous skin diseases, affecting all ages, with a prevalence of 2-5% in children. [32] AD is an inflammatory, relapsing-remitting skin disease, that heavily affects the QoL of patients and caregivers. It is recognized that a large majority of the forms of atopic dermatitis (AD) are associated with a concomitant sensitization to HDM or food allergens (so-called extrinsic AD). Starting from this observation, the possible use of AIT in AD was envisaged since many years, but the results of trials although overall favorable do not allow a formal indication. [33-35]. In fact, it is still controversial whether AIT may be beneficial for patients with AD. Considering the clinical effectiveness of AIT in IgE-mediated allergic diseases, several trials, often uncontrolled, investigated the efficacy of AIT for patients with “extrinsic” AD and reported overall controversial results [36-40]. It is true that robust and well methodological defined proofs of the clinical efficacy in extrinsic AD together with a demonstrated dose dependency effect are available [39, 41], but so far no clear indication or recommendation can be made. The use of AIT in AD remains experimental and the indications are confined to allergic rhinitis/asthma, when concomitant AD is present.

6. MECHANISMS OF SLIT AND BIODISTRIBUTION ASPECTS

AIT induces a multifaceted response, involving multiple components of the immune response to allergens and does not act on a single mediator or receptor [42, 43]. Thus, it is not possible to provide exact pharmacokinetic and pharmacodynamic data, rather only biodistribution characteristics. The first detectable effects appear after allergen tablets are put and held under the

tongue for at least 2-3 minutes and involve Langherans cells, which participate to the differentiation of naïve T cells to regulatory T cells (Treg cells). Tregs play a fundamental role in limiting the expansion of the classic allergic response, which is classically driven by Type 2 Helper (TH2) lymphocytes, by reducing TH2 response and, consequently, TH2-mediated production of IgE. The allergen-IgE-mast cell complex is the triggering event of allergic reactions, starting the subsequent inflammation that lasts until allergen exposure persists. EMA guidelines suggest that, albeit the possibility of considering AIT products as drugs in a true acception, to show their efficacy on the immune system IgE levels, interleukins concentration and T-cells responses should be monitored exhaustively. [44]. Current evidences show a weak correlation between the efficacy of AIT and specific IgG₄ level and their inhibition of the IgE-facilitated antigen presentation [45]. However, concerning HDM allergy, Nolte et al. assessed specific IgG₄ serum levels in a 24-week phase II trial and noticed a dose-dependent increase in those subjects receiving HDM-SLIT tablets as compared to placebo. [25] Further investigations are needed.

Concerning biodistribution and fate of an administered allergen product, only few studies in humans are available. Bagnasco et al, using I123 radiolabelled parietaria and HDM allergens and allergoids, showed that no direct or rapid absorption of the product (SLIT drops or tablets) occurred at sublingual level, and that a small fraction of chemically modified allergoids could be detected intact in the bloodstream. [46, 47]

7. CONCLUSIONS

In the field of HDM allergy MK-8237 clearly represents a step forward in clinical application of AIT, as demonstrated by the registration of grass tablets in Europe and US. The next GINA update will reconsider AIT, in the light of MK-8237 specific data in asthma. The definition of the predictive biomarkers of response to AIT is still an unmet need, but when available, it will further promote its clinical use.

8. EXPERT OPINION

Not all allergic patients respond to therapies, including AIT, in the same ways. Nonetheless, AIT represents a good approach to personalized medicine, since the mechanisms of disease and the mechanisms of action of treatment are well known and, in addition, detailed diagnostic tests are available. This is a good example of the transition from a population-based to a precision medicine. Previous therapies were unspecific and symptomatic, but a consistent number of patients did not show good clinical responses. In the next years we'll be moving to Precision Medicine, individually-targeted therapies directly acting on the specific physiopathological mechanisms of diseases, ideally reducing the number of subjects who do not have significant clinical response to current therapies. One of our aims was to emphasize on this point, on the need of selecting patients to address them to their right therapeutical approach, from which the more consistent outcome could be expected. [48, 49] Selecting patients appropriately will represent a turning point because from the choice of the rightest therapeutic pathway for each patient will depend treatment's efficacy. Other routes of administration of specific immunotherapies are undergoing evaluation and might help satisfy these unmet needs. [50] However, the evidence in literature about this aspect is still inconclusive. [51]

Intralymphatic immunotherapy (ILIT) [52, 53] and epicutaneous immunotherapy (EPIT) [54] are currently under investigation and good safety and efficacy profiles are emerging from the preliminary studies and clinical trials. Further studies are needed to better define these aspects.

One criticism on AIT efficacy is traditionally the lack of predictability. It is still unmet the need for a precise biomarker which would ideally bring an input in physicians choice and yield treatment's results predictable. Current evidences underline the potential role of TH2 inflammation molecules as useful biomarkers, suggesting that dosing IgE levels, interleukins concentration and T-cells responses should be monitored exhaustively. Recently, researchers attention has focused on specific IgG₄ levels, but without univocal results so far. Further investigations are needed.

The new HDM SLIT tablet MK-8237, recently approved and commercialized, represents a true advance in the field of allergen immunotherapy for house dust mite-induced allergic rhinitis and asthma, following the steps of the already consolidated data on grass pollen sublingual preparations. In fact, MK-8237 covers the need of an immunotherapy treatment for HDM allergy with a well defined and standardized maintenance dose that has been assessed by large dose-ranging studies. In addition the clinical efficacy of the product has been demonstrated not only for allergic rhinitis but also for asthma, that is usually more complex to assess and treat. This will change the attitude towards the clinical use of AIT in different parts of the world. On the other hand, although encouraging results are available for HDM sublingual tablets utilization in atopic dermatitis, no conclusive data on this topic are yet available, for the herein reviewed and other products and consequently need further investigations.

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Declaration of Interest:

GW Canonica has been a member of the advisory boards as well involved in scientific meetings for GlaxoSmithKline, Teva Pharmaceuticals, Sanofi Aventis, Roche, Novartis and AstraZeneca. Furthermore, P Giovanni is a consultant and speaker for ALK-Abello, AstraZeneca, Lofarma, Novartis and Stallergenes-Greer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

TABLE 1

A table highlighting data of the studies on HDM-SLIT tablet application in allergic rhinitis.

TABLE 2

A table highlighting data of the studies on HDM-SLIT tablet application in allergic asthma.

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• **A recent paper on the possibility of using ILIT as an alternative way of administering AIT.**

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• **A recent paper highlighting the possibility of adopting alternative ways of administering AIT.**

[illegible]

MT-06 (Demoly 2015) [27]	12 SQ-HDM	318 (100)	284 (89)	213 (67)	681 (100)	18	-1.22 (-1.96 to -0.49)	0.001	TCRS end of trial-1 year (total
	6 SQ-HDM	336 (100)	297 (88)	212 (63)	678 (100)	18	-1.18 (-1.91 to -0.45)	0.002	combined rhinitis symptoms)
	PLACEBO	338 (100)	296 (88)	154 (46)	327 (100)				
	ACTIVE	654 (100)	581 (88)	425 (65)	1359 (100)				
	OVERALL	992 (100)	877 (88)	579 (58)	1686 (100)				

TABLE 1 HDM-SLIT studies in Allergic Rhinitis

		N° PATIENTS (%)		N° A.E. s	DIFFERENCE FROM PLACEBO			
STUDY	TREATMENT GROUPS	N° (TOTAL)	N° (COMPLETING STUDY)	N° (%)	RELATIVE	ABSOLUTE (95% CI)	p-VALUE	ENDPOINTS
NCT00389363 (Mosbech 2014) [30]	6 SQ-HDM	156 (100)	140 (90)	103 (66)	mean 42%, median 50%	CI are not available in the study	0.0011	ICS dose reduction after 1 year
	3 SQ-HDM	159 (100)	134 (84)	106 (67)	mean 27%, median 25%	CI are not available in the study	0.91	treatment with SQ-HDM
	1 SQ-HDM	146 (100)	132 (90)	81 (55)	mean 35%, median 33%	CI are not available in the study	0.023	
	PLACEBO	143 (100)	126 (88)	77 (54)				
	ACTIVE	461 (100)	406 (88)	290 (63)				
	OVERALL	604 (100)	532 (88)	367 (61)				

MT-04 (Virchow 2016) [31]	12 SQ-HDM	282 (100)	248 (88)	130 (46)	24	-0.66 (-0.93 to -0.43)	0.02	Time to first moderate to severe
	6 SQ-HDM	275 (100)	237 (86)	107 (39)	24	-0.69 (-0.96 to -0.49)	0.03	asthma exacerbation during the
	PLACEBO	277 (100)	257 (93)	48 (17)				ICS dose reduction after 2 years of
	ACTIVE	557 (100)	485 (87)	237 (42)				treatment with SQ-HDM
	OVERALL	834 (100)	742 (89)	285 (34)				

TABLE 2 HDM-SLIT studies in Allergic Asthma

Drug Summary Box

Drug name	MK-8237
Phase	Launched
Indication	Allergic asthma, Allergic rhinitis
Pharmacology description	Immunostimulant
Route of administration	Sublingual
Pivotal trial(s)	[24][25][27][30][31]

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