

The Bioavailability of Allergens in Allergy Tablets Depends on Several Factors

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Dear Editors,

Ohashi-Doi et al. [1] recently investigated the kinetics of allergen release from house dust mite (HDM) sublingual allergen immunotherapy (AIT) tablets that are commercially available from different manufacturers. They concluded, solely on the basis of in vitro dissolution data, that (i) the allergen bioavailability relies on the tablet formulation, and (ii) only freeze-dried versus compressed tablets provide maximal release of soluble allergens following sublingual administration.

Sublingual AIT is an established, valid option for treating allergic respiratory diseases [2]. It consists of administering allergen extracts, either as a solution or a tablet under the tongue, to ensure mucosal delivery of the allergens. The allergens cross the oral mucosa, before being captured by resident antigen-presenting cells (APCs) which subsequently migrate to draining cervical lymph nodes to elicit allergen-specific Th1/Treg responses, thus suppressing the established allergic Th2 responses [3, 4].

With this aim, sublingual, fast-dissolving HDM tablets (Actair®, Stallergenes Greer, Antony, France) have been designed to sustain allergen release within 2–3 min, in order to promote allergen uptake by the

APCs (i.e., Langerhans cells) while preventing any sudden triggering of local pro-inflammatory cells (i.e., mast cells) [5]. It is recommended that the tablet be held under the tongue until it has completely disintegrated, and to then swallow and wait for 5 min before eating or drinking [6, 7]. As of today, 3 sublingual HDM tablets from 2 manufacturers are available on the market, Actair® from Stallergenes Greer, and Acarizax® and Miticure® from ALK A/S (Hørsholm, Denmark), based upon successful phase III clinical trials [8–11]. However, no superior clinical efficacy of one of these HDM tablets can be inferred because the efficacy of each was confirmed in separate clinical trials.

In this context, allergen bioavailability within the sublingual mucosa is of importance as it relates to both the safety and efficacy of AIT products. According to the European Medicines Agency: “Bioavailability means the rate and extent to which the active substance or active moiety is absorbed from a pharmaceutical form and becomes available at the site of action” [12]. Therefore, any rigorous assessment of the allergen bioavailability in sublingual AIT tablets should encompass not only (i) allergen content and release kinetics following

dissolution, but also (ii) the impact of saliva on allergen degradation, and, importantly, (iii) the analysis of allergen uptake by sublingual/oral epithelial cells and APCs.

Ohashi-Doi et al. [1] compared the 3 aforementioned HDM AIT tablets only in terms of the kinetics of allergen release, and there was evidence of distinct dissolution properties in vitro. Specifically, HDM major allergen release is faster for Acarizax® and Miticure® than it appears to be for Actair®. It is worthy of note that an in vitro dissolution assay performed according to the European Pharmacopoeia (Ph. Eur. 2.9.3 dissolution test for solid dosage forms, apparatus 4 flow-through cell) showed that 85% of total allergenic activity is released from Actair® 300 IR tablets within 2 min (data not shown). This confirms an appropriate release of major allergens and also that, when dissolution assays are performed by different methods, the results can differ dramatically. The latter conclusion also applies to major allergen assays. In any case, in vitro dissolution assays cannot be used as a surrogate of bioavailability unless an in vitro/in vivo correlation (IVIVC) is established (not the case in the study by Ohashi-Doi et al. [1]).

The impact of saliva on allergen integrity should also be taken into account, given that several constituents of saliva (>3,000 distinct proteins including enzymes, hormones, antibodies, and cytokines) [13] may induce allergen degradation, decrease allergen potency, and preclude optimal targeting onto epithelial cells and APCs. As demonstrated by Allam et al. [14], the kinetics of allergen uptake by oral human APCs are dose-dependent up to the point of saturation, and therefore represent a key factor contributing to allergen bioavailability.

Complete release of HDM major allergens within 30 s (as with Acarizax® and

Miticure®), instead of within minutes (with Actair®), could contribute to a faster allergen saturation of APCs, thus precluding optimal allergen targeting. The uptake and fate of allergens following sublingual administration should thus be monitored in appropriate preclinical models.

In summary, the bioavailability of allergen products, in particular HDM sublingual tablets, cannot be compared solely on the basis of in vitro dissolution assays in the absence of an established IVIVC. We also acknowledge the need to assess allergen bioavailability by multiparameter approaches, taking into account the peculiar features of the sublingual mucosa (e.g., sa-

liva components and uptake by oral APCs). For these reasons, one cannot infer that only freeze-dried tablets would provide an optimal release of soluble allergens for efficacious sublingual AIT. Collectively, novel approaches for the evaluation of allergen bioavailability are needed in order to design innovative formulations of AIT products.

Disclosure Statement

All authors are employed by Stallergenes Greer.

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