

EDITORIAL

The efficacy of oromucosal immunotherapy in respiratory allergy

While specific allergen immunotherapy (SIT), administered by subcutaneous injection is now widely recognised as efficacious, oromucosal immunotherapy has been slower in establishing its credentials. In part, this may be attributed to a lack of consensus in clinical trials with regard to administration methods and dosage schedules [1]. Trials using the oromucosal route can be classified under four different headings: (1) oral SIT with gastric absorption in which the vaccine is prepared as drops, capsules or tablets and is immediately swallowed; (2) oral SIT with enteric absorption in which the vaccine is modified to allow delivery of antigen only to the small intestine, thereby avoiding degradation in the stomach; (3) sublingual-swallow, in which the vaccine is held sublingually for 1–2 min and then swallowed with subsequent gastric absorption; and (4) sublingual-spit, in which the vaccine is held in the mouth for 1–2 min and then spat out. Extracts are administered daily or on alternate days during the induction phase, and weekly or twice weekly during maintenance treatment.

Acceptance of oromucosal immunotherapy has been additionally hampered in the past by clinical trials that have tended to be small-scale and have shown methodological flaws [2–5]. The WHO Position Paper, 'Allergen immunotherapy: therapeutic vaccines for allergic diseases' [6], published in 1998, found that there was no data showing that sublingual-spit immunotherapy was effective [7]. It did accept that a number of properly conducted double-blind, placebo-controlled trials have shown clear evidence as to the clinical effectiveness of sublingual-swallow immunotherapy with grass, *Parietaria* and mite vaccines [8–11]. More recent research is now available which further demonstrates the efficacy of sublingual-swallow immunotherapy in seasonal rhinitis to grass pollen [12,13], and *Parietaria* [14].

Controversy still remains with respect to the dose, although the most convincing clinical evidence supports the use of high-dose regimens. The optimal dose probably ranges between 5-fold and 100-fold the dosage of a standard course of subcutaneous SIT, and prolonged courses of therapy appear to be more effective than short ones [13,15–19].

Oromucosal immunotherapy is relatively safe. The most common side-effects reported are abdominal pain and oral/sublingual itching [10,20]. No severe adverse reactions have been reported, giving this form of immunotherapy a

definite advantage over traditional subcutaneous therapy [21,22].

Little is known about the pharmacokinetics for local immunotherapy. The information that is available tends to be obtained from animal models and often is non-conclusive. Bagnasco *et al.* studied the kinetics of the radiolabelled *Parietaria judaica* major allergen (Par j 1), after sublingual and oral administration in healthy volunteers [23]. With the oral route, the radiolabelled allergen was rapidly detected in the stomach and small intestine. No scintigraphic evidence of radioactivity accumulation at specific sites corresponding to any defined lymphatic structure was detected.

The sublingual route showed an identical distribution once swallowed, but interestingly, a significant amount of radiolabelled allergen persisted at the sublingual level for up to 20 h. This represented about 2% of the dose and resisted extensive mouth rinsing. Perhaps less surprising given the lack of efficacy seen with sublingual-spit immunotherapy, there was complete absence of absorption of the radiolabelled allergen through the sublingual mucosa to the bloodstream for up to 30 min. In the clinical setting, the allergen would be held under the tongue for only 1–2 min. Consistently, plasma radioactivity increased only after swallowing. Nevertheless, it is possible that slow absorption and processing of the locally retained allergen occurs through the local immune system.

The scientific basis of local administration of allergen extracts on mucosa relies on the concept of inducing local tolerance. Although the mechanisms remain poorly understood, dendritic cells, derived from the mucosa of the gastro-intestinal tract are thought to act as antigen-presenting cells [24]. They also produce IL-12 which promotes the development of Th1 over Th2 cells [25–27]. A number of studies have also demonstrated a marked increase in allergen-specific IgG and IgG4 antibodies [28,29], and more recently an additional response in IgE antibodies as well [10–13,30].

In this month's issue of *Clinical and Experimental Allergy*, Bagnasco *et al.* develop their work further with a report on the pharmacokinetics of an allergen and a monomeric allergoid [31]. The carbamylated monomeric allergoid derived from *Parietaria judaica* major allergen (Par j 1) and the native allergen were radiolabelled with ¹²³I. Both preparations were given to allergic subjects and, unlike their previous study, the administration followed

usual clinical practice in that the compound was retained under the tongue for only 1–2 min before being swallowed.

As in the previous study, plasma radioactivity started to appear only after swallowing. The plasma peak occurred at 2 h and was higher with the allergoid tablet preparation compared to the native allergen. This slight difference in kinetic profile may be explained by an increased resistance in the allergoid to gastrointestinal enzymatic degradation. The authors postulate that it may occur as a result of the substitution of the majority of $-H_2$ residues, which are necessary for the hydrolytic action of many enzymes. The modification process does not appear to affect the capacity of the allergoid to evoke a specific antibody response against the non-modified allergen.

This is an important finding, as one of the main reasons that oral immunotherapy has not been widely accepted, is the lack of potency of allergens given by this route. As discussed earlier, in order to achieve either a serological or a clinical response, oral doses of allergen have tended to be many times the cumulative dose required by the subcutaneous route. The reason for this is thought to be the destruction of allergens in the stomach by acid and pepsin, and subsequent intestinal enzymatic degradation of the allergen, reducing its antigenicity further. Modified allergen preparations may in future make it possible to achieve the same clinical benefit with lower antigen doses via the oromucosal route.

As in Bagnasco's previous work, some persistence of both the radiolabelled allergen and allergoid was observed in the mouth. In this study, the tracer could be detected for up to 2 h while in the previous study, the persistence was longer. This is probably a result of the different preparations used, and the different time intervals that the preparation was kept sublingually. The reproducibility of local persistence of allergen raises interesting questions about the mechanisms of action of oromucosal SIT, and may add weight to the hypothesis that allergen can gain access to Langerhans' cells within the sublingual mucosa.

What is clear from this study is that, in sublingual-swallow immunotherapy, the main route of absorption is the gastrointestinal tract, and that the allergoid preparation is probably more efficiently absorbed compared to native allergen. Further studies are clearly needed to understand the kinetics of oromucosal immunotherapy better, and to develop more sophisticated methods of allergen delivery via this route.

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