SUBLINGUAL IMMUNOTHERAPY: ADMINISTRATION, DOSAGES, USE

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Allergen extracts for sublingual immunotherapy (SLIT) are currently marketed by several manufacturers, with administration schedules and amount of allergen(s) quite variable in the different products, although almost all are standardized biologically or immunologically. The allergen extracts for SLIT are available in two main pharmaceutical forms: solution to be delivered by drop-counters, pre-dosed actuators (mini-pumps) or disposable single-dose vials; tablets with appropriate composition that allows a slow (1-2 minutes) dissolution in the mouth in contact with saliva. In Europe, SLIT is prescribed in general for one or a few allergens, and mixtures are less used, though there is no immunological contraindication to give multiple allergens. SLIT traditionally involves a build-up phase and a maintenance phase with the top dose. The build-up phase has usually the duration of 4 - 6 weeks. The patient must start with the lowest concentration and gradually increase, using the different dosage preparations, until the maintenance dose is reached. Rush and ultra-rush inductions have been introduced, based on the safety profile of SLIT that is very favorable. For these reasons it has been suggested that a an updosing phase maybe even not necessary. The no-updosing approach would result in a treatment that is more patient-friendly and convenient to manage. Indeed, the most recent randomized trials were performed with the no-updosing regimen and their results in term of safety were as favorable as the studies performed with the traditional updosing approach. The currently recommended duration of SLIT is comprised between 3 and 4 years depending on the clinical response in single patients.

In Europe, allergen extracts for sublingual immunotherapy (SLIT) are currently marketed by several manufacturers, thus the administration schedules and amount of allergens are quite variable in the different products. However, almost all the SLIT vaccines commercialized in Europe are standardized biologically or immunologically (1). The standardization methods are still largely based on in-house references, thus the extracts are labeled in units that differ from manufacturer to manufacturer. Some of the most used labeling units are: Allergen Units (AU), Index of Reactivity (IR), Biological Units (BU), Standard Units (STU). On the other hand, during the last few years the availability of the content in micrograms of the major allergens have represented a significant improvement, since this allows to roughly compare the different therapeutic regimens. In general, the dose of allergen given in a SLIT course is 5-300 times higher (again, according to the manufacturer) than in the correspondent subcutaneous immunotherapy (SCIT) so that the term high-dose SLIT is somewhere used to indicate this treatment (2).

The allergen extracts for SLIT are available in two main pharmaceutical forms: a) solutions to be delivered by drop-counters, pre-dosed actuators (mini-pumps) or disposable single-dose vials; b) tablets with appropriate composition that allows a slow dissolution in the mouth in contact with oral mucosa.

Concerning the US market, the American Medical Association's Current Procedural Terminology 2005 manual defines immunotherapy as "parenteral administration of allergenic extracts as antigens at periodic intervals" (3), therefore there are no FDA-licensed products for SLIT in the United States.

PRACTICAL ADMINISTRATION

The allergen extract, in solution or tablets, is usually administered in the morning before breakfast. The drops

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or tablets are kept under the tongue for 1-2 minutes and then swallowed (sublingual-swallow method). In some studies the allergen was kept under the tongue and then spat out and this technique is called sublingual-spit (4,5). Considering pharmacokinetics studies performed with radio-labeled allergens (6), it was found that, after spitting, a relevant amount of the allergen remains in the mouth. According to this observation and based on practical considerations of convenience and simplicity, the sublingual-swallow method is now considered the most appropriate and, therefore, is universally used in clinical trials and practice. The acronym SLIT, unless otherwise stated, indicates the sublingual-swallow modality.

In the last years there was a renewed interest in the use of tablets and recent large trials were all performed with this preparation (7,8). Tablets are simpler to take than solutions, and their time of dissolution in the mouth can be fixed by an adequate formulation, but they cannot be divided. Taking into account the advantages and the possible disadvantages it is likely that soluble tablets will be in the future the most suitable way of administration.

In Europe, immunotherapy in general is prescribed for one or few allergens, and mixtures are less used than in the USA, although there is no immunological contraindication to give multiple allergens also with SLIT. A recent study has shown that SLIT treatment with a mixture of grass and birch was more effective than the single allergens alone (9). On the other hand, the co-administration of numerous extracts mixed together, in the case of adverse events, makes difficult the identification of the responsible extract. In addition, two cases of anaphylaxis recently described were provoked by heterogeneous mixtures of more than four different allergens given together (10,11).

ADMINISTRATION REGIMENS

SLIT traditionally involves a build-up or updosing phase (with gradually increasing doses) and a maintenance phase with the top dose (12). The build-up phase has usually the duration of 4-6 weeks. The extract is therefore prepared in separate vials (or in separate blisters of tablets) at different and increasing concentrations. The patient must start with the lowest concentration and gradually increase, using the different dosage preparations, until the maintenance dose is reached. Rush and ultra-rush inductions have been proposed, based on the safety profile of SLIT that is very favorable, also in children under the age of 5 years (13-14). Ultra-rush schemes with a build-up shorter than 2 hours has been reported in adults (15) and children (16-17), with favorable results. For these reasons it has been suggested that a an updosing phase maybe even not necessary (18). The no-updosing approach would result in a treatment that is more patient-friendly and convenient to manage. A randomized trial directly compared the safety of the traditional updosing regimen with the no-updosing in 135 patients and found no difference in the rate and type of adverse events with the two different approach (19). There was indeed a single report of anaphylaxis with an ultra-rush updosing with latex extract (20), therefore, caution should be taken during the induction phase with this allergen.

The maintenance dose is generally the same for all patients and it is identified by the manufacturer, based on clinical results. The use of the same dose for all patients is justified by the fact that, differently from subcutaneous immunotherapy, also the administration of very high amounts of allergens does not provoke severe side effects. In one dose-finding study, one of the groups of patients received an amount of 1,000,000 Standardized Quality Units per day, which correspond to 200 mcg of Phl p 5 allergen (21). It was observed a certain dose-dependency of side effects, but even with the higher amount of allergen, the side effects were mostly local (oral itching/swelling) and mild or moderate. The same results were reported also in patients suffering from asthma (22). Thus far, we do not know which is the dose that invariably provokes severe side effects, and this dose is conceivably much higher than the doses usually administered.

The maintenance dose can be administered at time intervals that are variable among manufacturers. For instance, once daily (23), on alternate days (24), or once weekly regimens (25) have been proposed. Nowadays, the general trend is to simplify the regimen by giving the maintenance dose once daily, as done with almost all drugs.

CRITERIA FOR STARTING AND STOPPING

SLIT can be administered either pre-co-seasonally (stop at the end of the season) or continuously. Pre-co-seasonal schedules are commonly used for pollen allergy. In this case the treatment starts 2-3 months before the expected pollen season. In the pre-co-seasonal regimen, no dose reduction during the pollen season is usually applied. On the other hand, for nearly-perennial or perennial allergens, a continuous treatment is preferred. A recent study evaluated in patients allergic to dust mites the possibility to use a SLIT schedule with intermittent (i.e. 2-month treatment alternating with 2-month suspension) administration of the mite extract, with comparable safety in respect to the continuous daily administration (26).

There is no published randomized controlled study on the optimal duration of a SLIT treatment, although long lasting clinical effects were reported with a 4-5 year course of treatment both in children (27) and adults (28). Since these evidences are insufficient, the recommendation for

the duration of SLIT must necessarily derive from the SCIT experience as reported in consensus documents (29-30). This implies that a SLIT course should be continued for 3 to 5 years to expect log lasting efficacy, but discontinued if there is no benefit after 2 years of treatment.

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