

## Clinical process to properly prescribe immunotherapy

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## PART I

### Correct diagnosis

The clinical process to properly prescribe allergen specific immunotherapy (ASIT) starts with a correct diagnosis of an IgE mediated reaction as the cause of the patient's symptoms. The presence of an IgE mediated hypersensitivity reaction in a patient with clinical signs and symptoms of allergic rhinoconjunctivitis and/or asthma (and/or atopic dermatitis) can be confirmed with in vivo or in vitro testing.<sup>1-3</sup>

For the in vivo testing the most used method still today is the skin prick test, eventually extended with an intradermal test. However, the latter only adds some diagnostic value in the case of weak diagnostic extracts.<sup>4-5</sup> Intradermal testing after a negative SPT with a potent extracts, such as a pollen extract in the US, does not add any diagnostic accuracy and thus is not recommended, as the ratio of false positive reactions with an ID test in this scenario is high.<sup>1</sup>

Among the in vitro test methods the detection of specific IgE against certain allergens is –at world level- still mostly done with the RAST, Immulite or ImmunoCAP systems. These methods are generally applied for the detection of specific IgE directed against whole allergens. However, newer more specific methods are underway and already on the market in some European countries (very limited in US) that have the potential to detect specific IgE directed against certain epitopes of the allergen. As such, these methods are able to reveal the presence and quantity in patient's serum of highly specific IgE against e.g. Phl p 1, Phl p 2, Phl p 5, etc. instead of only measuring the global IgE against *Phleum pratensis*. Microarrays are used for these highly specific diagnostic procedures.<sup>6-7</sup>

However, the sole presence of IgE mediated hypersensitivity is not enough to justify the prescription of ASIT. Two other components are needed to this end:

- 1) Symptoms of the patient on exposure: a detailed anamnesis is a core tool for the allergist<sup>2-3, 8</sup>
- 2) AND (one of the following)
  - Poor response to pharmacotherapy, allergen avoidance, or both;
  - Unacceptable adverse effects of medications;
  - Wish to reduce or avoid long-term pharmacotherapy and the cost of medication;

- Co-existing allergic rhinitis and asthma;
- Possible prevention of asthma in patients with allergic rhinitis. This indication has been included officially in the WAO statement on sublingual immunotherapy.<sup>9</sup>

Typical indications for SCIT are allergic rhinitis, allergic conjunctivitis, allergic asthma and systemic reactions after exposure to hymenoptera venom. New indications for SCIT are atopic dermatitis in individuals with aeroallergen sensitization and patients who experience recurrent bothersome large local reactions to hymenoptera venom. Though in previous versions of the practice parameters SCIT was not recommended for children below five years of age, in the 3<sup>rd</sup> update of the PP it is stated that there is no specific upper or lower age limit for initiating allergen immunotherapy.<sup>3</sup>

### **ASIT is indicated, and now...**

After a correct diagnosis and the decision to start ASIT in a patient, the allergist has to face the next set of challenges:

1. Which route: sublingual or subcutaneous?
2. Which allergens to include in the immunotherapy? Mono- or multi-allergen ASIT?
3. In case of multi-allergen ASIT: which allergens can be mixed together in one vial?

To answer these questions, differences between continents in the practice of immunotherapy must be taken into account. There exist several differences between Europe and North America in the details concerning immunotherapy preparation and application.

1. There is no FDA approved extract for sublingual immunotherapy
2. In North America the allergist in his office prepares vial for immunotherapy, from which the patient shall receive his/her injections.
3. Immunotherapy is generally given with a mixture of several allergens.
4. Immunotherapy is given with natural, aqueous extracts. There are neither allergoids nor depot extracts in the US.

#### **Ad 1. Sublingual or subcutaneous immunotherapy**

The first decision to be made is about the route of administration. In the US SIT is almost exclusively given as SCIT, because till now there are no FDA approved extracts for SLIT. Even so, a survey among US allergists in 2006 showed that 6% is applying SLIT, using the SCIT extracts.<sup>10</sup> Clinical trials of SLIT have been ongoing the last years in the US. At first they were not too successful.<sup>11</sup> but lately good results have been reported, both in adults<sup>12</sup> and in children.<sup>13</sup>

In Mexico and most Latin American (LA) countries both administration routes are available and used by many allergists. (See poster Gómez M, WAC 2011) The sublingual route is especially popular for the application of SIT in (small) children, in patients with particular risk-factors for SCIT, in situations where it is not feasible for the patients to come to the clinic and in some adults who prefer to omit the many office visits for the application of

their injections. As such, SLIT and SCIT are considered complementary in LA, as SLIT broadens the market for immunotherapy in general.

Recently, a group of experts cooperated in the development of WAO guidelines on SLIT. Chapter 9 of this document is on the indications for SLIT.<sup>14</sup>

## **Ad 2. Preparation of immunotherapy in the allergist's office**

In North America part of the allergist's training is how to prepare allergen immunotherapy.<sup>15</sup> Several points of interest have to be taken into account to adequately prepare a SIT vial, some of which might also apply to the European allergist.

### ***Selection of the allergen(s) to be included in the treatment***

#### Clinically important allergens

Skin prick testing and/or the detection of specific IgE in the patient's serum by Immulite or ImmunoCAP may yield a certain amount of positive results, demonstrating the presence of specific IgE against several allergens. An essential task for the treating allergist is to determine which of these allergens is/are of clinical importance and reduce their number as much as possible. Immunotherapy seems to be more effective, if given with only a few allergens see below.

#### Cross reactivity

Apart from the selection the allergens for immunotherapy, based on their clinical importance, the number of allergens to be included in the immunotherapy vial can be further reduced taking into account the cross-reactivity between certain allergens, especially those of the same genus or family. Allergens phylogenetically close to one other' in some cases have a high number of similarities. As a consequence, selecting just one of them to cover sensitivities to any other member of the group is enough. This holds especially true for the pollens of certain families of grasses and trees. An excellent review on this subject can be found in two references.<sup>16-17</sup>

#### Proteases

A third rule for the mixing of allergens in one vial has to be taken into account: it is recommended not to put allergens rich in proteases (e.g. molds, cockroach) in the same vial together with allergens with a low concentration of proteases (e.g. grass pollen). Especially for timothy grass pollen it has been shown that mixing with mold extract reduces the detectable amount of allergen after a short while.<sup>18</sup>

### **Immunotherapy with mixes of allergens**

A still ongoing point of discussion is the mono- versus multiple allergens SIT, with the former being practiced in Europe and the latter being the way SIT is given in 'the Americas'. Those in favor of the mono-allergen SIT, argue that almost all studies on SIT have been done this an extract of just one allergen and that in most patients treatment with just one -or may be two unrelated- allergen(s) is enough to cover all clinically relevant allergens.

However, those in favor of multiple allergen SIT argument that almost all patients are not only multi-sensitized (=skin prick sensitivity to various non-related allergens), but truly multi-allergic. Moreover, they say, the very first double blind clinical trials showing efficacy for SIT were done with allergen mixes (Johnstone et al 1961<sup>19</sup>; Franklin et al, 1967<sup>20</sup>).

This kind of discussions is interesting, because they show us the multiple faces of allergy: in some areas clear 'hay fever' may exist, as in North and Central Europe, with well-defined pollen seasons of short duration. In this kind of patients surely a mono-allergen SIT is a wonderful solution. However, in other parts of the world -like in some states of the US and many countries of LA- it is rare to find this typical hay fever patient, as pollen is in the air all year long. Moreover, the closer to the equator the higher the concentrations of several species of house dust mite and in the humid sub-tropical areas molds are everywhere. So the allergic patient in these places has a totally different picture of sensitizations and allergies than patients from the aforementioned zones. As a result, immunotherapy probably shall have to be different to be efficacious.

An interesting SLIT study was done in at National Jewish in Denver<sup>21</sup> rising doubts about the efficacy of multi-mix SLIT: the mono-allergen SLIT performed quite better than the multi-mix SLIT, even though the allergen concentration was kept stable.

### **Allergen extracts in the US: natural and aqueous**

In the US the only extracts on the market are concentrated, aqueous solutions of allergens, meant to be diluted before they can be administered to the patient. A couple of years ago, there were some trials on allergens coupled to adjuvants. One of those molecules is Tolamba, the ragweed pollen major allergen, covalently coupled to Toll-like receptor agonists. However, the FDA has not accepted this kind of immunotherapy yet. For the moment, neither recombinant allergens nor allergoids are used for SIT in the US.

Some European allergen manufacturers have managed to bring their products on the market in some LA countries. Even so the mainstay of SIT in LA is still with aqueous extracts that are mixed in the allergist's office (although there are some exceptions). In Mexico there exist three different categories of commercial allergens: those imported by some Spanish allergen manufacturers and sold as such as end-product; those imported as lyophilized products from raw material providers in the US and sold on the Mexican market unstandardized and the locally manufactured products.<sup>22</sup> There is a wide variety in the potency of these three categories<sup>23-24</sup>

## **PART II**

### **Allergen dose**

Allergists prepare the immunotherapy solution in their offices from concentrated allergen vials. US and LA allergists have taken note of the few dosing studies there exist on Immunotherapy and believe that a certain minimum maintenance dose has to be reached, for IT to be effective.<sup>25</sup> Consequently, dosing recommendations exist for projected maintenance doses of each allergen. These doses are meant to be reached in 3-6 months, in a regular regimen. If the patient presents adverse reactions to the applications, it might even take longer before the maintenance dose is reached.

SIT is initiated routinely with approximately a 1/1000<sup>th</sup> or 1/10.000<sup>th</sup> of maintenance dose, some times amore diluted extract could be prepared pending on the intensity of ST reaction and slowly build-up with injections once or twice a week. At maintenance, injections are given each 2-4 weeks. The maintenance dose is that considered to provide efficacy without significantly local or systemic adverse reactions. Some patients will not tolerate de projected therapeutic dose and will have to be adjusted to the highest tolerated effective dose of each extract when mixtures are used. This concept does not apply to venom

immunotherapy which therapeutic dose has to be reached for conferring adequate protection.<sup>26</sup>

All dilutions can be calculated with this general formula:<sup>26a</sup>  **$V_1 \times C_1 = V_2 \times C_2$** .  
Were:  $V_1$  = Final volume you want to prepare;  $C_1$  = Final concentration you want to prepare (w/v, PNU, AU, etc.);  $V_2$  (unknown) = Volume of extract (from stock concentrate) you will need for dose required and  $C_2$  = Concentration of extract (from concentrate stock) you will use.

### Example 1.

Prepare 5 mL ( $V_1$ ) at 1:200 w/v concentration ( $C_1$ ) from a stock concentrate of 1:10 w/v ( $C_2$ ) =  $V_2$  (not yet known). We can use either one of the two options of formula composition depending if we are using w/v: [ $V_2 = (V_1/C_1) \times C_2$  if we decide no to change fractions for decimals.] or PNU, AU, BAU, etc. [ $V_2 = (V_1 \times C_1) / C_2$ ].

Inserting numbers or fractions to the formula, as we need.

$$V_1 = 5 \text{ mL}$$

$$C_1 = 1/200$$

$$V_2 = ?$$

$$C_2 = 1/10$$

$$V_1 \times C_1 = V_2 \times C_2$$

$$V_2 = (V_1/C_1) \times C_2 \quad (5/200) \times 10 = \mathbf{0.25 \text{ mL}}$$

$$\text{Plus diluent volume } (5\text{mL} - 0.25 \text{ mL}) = \mathbf{4.75 \text{ mL}}$$

### Example 2.

Prepare 5mL ( $V_1$ ) at 2000 AU concentration ( $C_1$ ) from a stock concentration of 10,000AU ( $C_2$ ) =  $V_2$  (unknown)

$$V_1 = 5 \text{ mL}$$

$$C_1 = 2000 \text{ AU}$$

$$V_2 = ?$$

$$C_2 = 10,000 \text{ AU}$$

$$V_1 \times C_1 = V_2 \times C_2$$

$$V_2 = (V_1 \times C_1) / C_2 \quad (5 \times 2000) / 10,000 = \mathbf{1.0 \text{ mL}}$$

$$\text{Plus diluent volume } (5.0 \text{ mL} - 1.0 \text{ mL}) = \mathbf{4.0 \text{ mL}}$$

If we need to prepare a mixture of compatible extracts, we have to keep in mind that we have to reach the projected therapeutic dose for each component extract and be aware of the dilution effect between each other.

### Example 3.

A total of 10 non-standardized pollen allergens producing positive skin tests have been selected as candidates for IT. The 10 allergens include:

5 trees: box elder, cottonwood, elm, maple, oak 2 grasses: Kentucky blue, timothy 3 weeds: lamb's quarter, pigweed, short ragweed

First, examine the 10 allergens for known patterns of cross- reactivity. Among the 5 trees, box elder and maple belong to the same genus and are highly cross-reactive. The same is

true for the 2 grasses, Kentucky blue and timothy grass. So we will keep only one of each (cottonwood, elm, maple, oak. grasses: timothy. weeds: lamb's quarter, pigweed, short ragweed).

Prepare 5 mL (V1) at 1:200 w/v concentration (C1) from a stock concentrate of 1:10 w/v (C2) = V2 (not yet known). Using w/v  $[V2 = (V1/C1) \times C2]$ .

Inserting numbers or fractions to the formula, as we need.

$$V1 = 5 \text{ mL}$$

$$C1 = 1/200$$

$$V2 = ?$$

$$C2 = 1/10$$

$$V1 \times C1 = V2 \times C2$$

$$V2 = (V1/C1) \times C2 \quad (5 / 200) \times 10 = \mathbf{0.25 \text{ mL} \times 8 = 2.0 \text{ mL}}$$

$$\text{Plus diluent volume } (5\text{mL} - 0.25 \text{ mL}) = \mathbf{3.0 \text{ mL}}$$

An individual approach is always recommended. For example, in a patient with four clinically relevant sensitizations e.g. cat, dog, olive pollen and grass pollen, the decision must be based on the allergen which causes:

1. The longest duration of symptoms per year; 2. The most severe symptoms; 3. A major impact on quality of life and 4. Which is more difficult to avoid.

In the previous example, the pet allergens could be avoided, whereas grass pollen is the allergen that has the longest duration of pollen season, however, in some regions the length of pollen season may vary.<sup>27</sup>

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