AAOA Consensus Sublingual Immunotherapy Dosing Protocol

Sublingual immunotherapy (SLIT) has recently gained a lot of attention as an alternate route of allergen delivery for immunotherapy, although the technique emerged in the early 1900s. SLIT was pioneered by physicians in the United States, but its widespread use has mainly been in Europe over the last 15 years. The AAOA recognized several years ago that our membership was becoming increasingly interested in the SLIT technique. This interest is also being realized in the general allergy community. For this reason, an intense review of the literature was undertaken in order to provide some direction to dosing in our membership who are interested in providing the option of SLIT to their patients. The findings of this literature review will be published as a supplement in the journal *Otolaryngology – Head and Neck Surgery*. The manuscript is in final stages of printing, and should be released in the next couple months. The assertions made in this article, are derived from our findings that will be published in the supplement, and will not be referenced separately here.

The leadership of the AAOA composed a panel of our membership who have experience using subliminal immunotherapy, or a firm knowledge of the SLIT literature. The panel of physicians met in September 2006. The goal of this panel was to derive a consensus protocol for SLIT dosing that could be provided to our membership. The literature does not provide for a dosing technique that could be called “standard”, yet it does provide a range of techniques which have shown efficacy and safety. The goal of the panel was to develop a dosing protocol that was within this range of techniques, yet able to easily blend into the techniques most otolaryngologists use for injection immunotherapy. The following protocol was agreed upon by this consensus panel, and the AAOA has begun teaching this technique at our allergy courses.

The escalation phase of sublingual immunotherapy is quite short compared to injection immunotherapy. The average escalation time is around two months. The vast majority of published clinical trials do not base the dosing of SLIT on quantitative allergy test results. In most published studies, the starting dose and escalation schedule is almost uniformly the same for all patients, regardless of degree of reactivity found in allergy testing. For this reason, the panel did not recommend the need for quantitative testing in order to start sublingual immunotherapy. Qualitative testing is sufficient to allow for safe dosing of sublingual immunotherapy. This is not to say that quantitative testing is not important, especially since the physician usually does not know if the patient will decide to try the sublingual or injection route of immunotherapy until after testing is done.

During both escalation and maintenance phases, sublingual dosing is once a day. He drops are to be applied under the tongue, and held there for two minutes. He drops are then swallowed. If two vials are necessary, due to the number of antigens being treated, the drops can be applied sequentially, or separated, with one vial administered in the morning, and the second vial administered in the evening. A 12 week escalation phase was decided upon. Four vials will be utilized during the escalation. The escalation vials will contain 5 mL of solution. Dosing from each escalation vial will begin with one drop daily for seven days, then increased to two drops for seven days, and finishing with three
drops for seven days (figure 1). After administering three drops daily for seven days, the vial is discarded, and the next escalation vial will then be started with the same pattern. This pattern will be repeated until the maintenance dose is reached with the fourth vial. Once three drops a day is reached with vial number four, the maintenance dose has been reached, and the patient can continue to use three drops daily until the fourth vial is depleted. All subsequent vials will be at maintenance concentration, and the patient will begin each vial with three drops, and continued this daily. The maintenance vials need to contain 10 mL of solution to allow for about three months duration for each vial.

**Figure 1: SLIT Escalation Scheme**

<table>
<thead>
<tr>
<th>Vial #1 (1:62,500)</th>
<th>Vial #2 (1:12,500)</th>
<th>Vial #3 (1:2500)</th>
<th>Vial #4 (1:500)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 drops</td>
<td>1 drop</td>
<td>1 drop</td>
<td>1 drop</td>
</tr>
<tr>
<td>2 drops</td>
<td>2 drops</td>
<td>2 drops</td>
<td>2 drops</td>
</tr>
<tr>
<td>3 drops</td>
<td>3 drops</td>
<td>3 drops</td>
<td>3 drops</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(maintenance dose)</td>
</tr>
</tbody>
</table>

**Doses are given once a day**

**Each step up lasts 7 days (i.e. 1 drop 7 days, then 2 drops 7 days, etc)**

1 drop = about 0.03 to 0.07 mL, depending on dropper design and bottle lot.

The panel decided to utilize 5-fold dilutions in preparing the allergy vials to keep this consistent with our practice in injection vial preparation. The SLIT escalation vial preparation is essentially the same as injection vial preparation. The maintenance vial preparation applies the same principles, but doubles the dose in order to allow for a 10 mL vial, which on average lasts nearly 3 months. The panel recommends mixing directly into dropper vials in order to avoid inadvertent injection of the sublingual solutions. 50% glycerin is used as the diluent. Since the drops are administered sublingually, this high concentration of glycerin will not cause pain like it can with injection. The high glycerin concentration improves the taste of the sublingual drops, and also helps preserve the antigenicity of the solution. This can allow for more convenient use with people who travel, and cannot keep the vials constantly refrigerated. Figure 2 illustrates the mixing technique for both the escalation, and maintenance vials.
Figure 2: **Sublingual Immunotherapy Vial Mixing Protocol**

### Escalation Dropper Vials – 5mL Vial

Make the first four dropper bottles at one time (will be numbered in reverse so #1 is first vial used by patient and is the most dilute)

Dropper vial #4 (This vial will contain maintenance dose concentration)
- Mix 0.2 ml of concentrate for each antigen to sterile vial
- Add enough 50% glycerin to make 5 ml of total volume

Dropper vial #3
1 ml of vial #4
+ 4 ml 50% glycerin

Dropper vial #2
1 ml of vial # 3
+ 4 ml 50% glycerin

Dropper vial #1
1 ml of vial # 2
+ 4 ml 50% glycerin

### Maintenance Dropper Vial – 10ml Vial

Mix 0.4 ml concentrate of each antigen (*) into dropper vial
Add 50% glycerin to total 10 mL volume

*Notice that compared to escalation, double the amount of each antigen concentrate is added, and the total volume is doubled. This results in the same maintenance concentration that was obtained for escalation vial #4.*

The 10 mL vial lasts almost 3 months for most dropper vials.

The AAOA considers this consensus SLIT dosing protocol to be within the range of published dosing techniques that have been shown to offer efficacy and safety. This protocol is being taught at the AAOA allergy courses, and will be utilized for future SLIT clinical trials planned by the AAOA in the future. This protocol will be utilized until future dosing studies can directly evaluate optimal dosing for sublingual immunotherapy.

It is important to interject at this point that the excellent safety profile that has been shown for SLIT does not mean there is not risk associated with this immunotherapy.
technique. There have been recent reports of anaphylactic reactions when sublingual immunotherapy was used for desensitization for Type 1 food allergies and latex allergies. I have also been informed of an anaphylaxis case with SLIT used for and inhalant allergen, but I have not seen the publication which reports this. The take-home message is that even though SLIT has demonstrated in good safety for inhalant allergens, appropriate caution is still advised. Great caution should also be exercised in utilizing SLIT for non-inhalant allergens, since the safety of SLIT for these allergens is not well reported on in the literature.