SUBLINGUAL IMMUNOTHERAPY (SLIT) UPDATE

Sublingual immunotherapy (SLIT) is a method of antigen- specific immunotherapy. SLIT is an alternative to the subcutaneous (injection) immunotherapy (SCIT), which is the dominant means of administering immunotherapy in the United States. In SLIT, immunotherapy is accomplished by exposure of the antigen to the floor of the mouth mucosa. Then, presumably via transmucosal and possibly lymphatic transport, the antigen is able to interact with the immune system. The SLIT technique has been used widely in other countries, particularly in European countries. Although the efficacy and optimal dosing ranges for sublingual immunotherapy have not been clearly identified in the United States, the safety of the technique has been widely accepted in the world literature. The safety of SLIT has been demonstrated in numerous European studies using both low and very high antigen doses. SLIT has been recognized as an acceptable means of antigen immunotherapy by the World Health Organization.

SLIT also has a long history of use in the United States, but with a much smaller group of physicians utilizing this technique. Increased interest in using the SLIT technique in the United States has been generated over recent years. The American Academy of Otolaryngic Allergy (AAOA) has attempted to provide information to the members about the reported safety, efficacy, and potential dosing schedules that are available in the literature. Until recently, there were no data available about dosing schedules utilizing antigens that are available in the United States. Although numerous dosing strategies have been published in the literature, the studies utilized antigen formulations that are not available in the United States. It is not possible to accurately or reliably convert the units of antigen measurement used in these studies to United States–based antigens.

Two years ago the AAOA presented a sample sublingual immunotherapy dosing schedule that was based on personal experience from physicians who had been using sublingual immunotherapy for many years, as well as information from European studies[1]. The dosing schedule presented was conservative in terms of antigen amounts and escalation duration in order to emphasize safety until a United States antigen dosing protocol was published. Recently, Greer has released data from United States-based sublingual immunotherapy studies that provides some objective dosing parameters to which we can compare the AAOA sample dosing schedule[2]. The AAOA Sublingual Task Force decided to reevaluate our sample dosing protocol based on the dosing information available in the Greer data. *It is important to stress that a universally acceptable dosing schedule for sublingual immunotherapy is not known at this time, and that there are no antigen products that have FDA approval for use in sublingual immunotherapy.* Furthermore, patients should be informed that the use of sublingual immunotherapy in United States is considered to be an off–label use of an FDA–approved antigen product, and that the optimal dosing ranges for individual antigens have not been determined.
It is also important to recognize that the vast majority of clinical information about sublingual *and* subcutaneous immunotherapy is based on studies using a single antigen only. It is not known if efficacy and dosing data that is derived from single- antigen immunotherapy studies can be extrapolated to multi-antigen immunotherapy. The optimal dose for an antigen included in a multi-antigen vial may be the same, lower, or higher than the dose that was determined by a single-antigen study.

The AAOA leadership has made the commitment to revise the course presentations regarding allergy management as information becomes available in the literature. With this in mind, alterations will be made to the sublingual dosing schedule that is presented at the AAOA courses. For those who have already attended AAOA courses where a sublingual dosing schedule was presented, the main changes will be in the amount of antigen that will be delivered each day, and the length of the escalation schedule. The new dosing schedule is based on Greer short ragweed data presented at an AAAAI meeting. The new dosing schedule will deliver a maintenance dose of 7 mcg of short ragweed standard antigen daily. This dose can be accomplished by adding 1 mL of standard 100,000 AU/mL ragweed antigen to 9 mL of 50% glycerin, and giving 0.2 mL daily doses. The escalation will occur over 10 days, and is meant to identify patients who will develop uncomfortable symptoms. The escalation vial is prepared by taking 0.25 mL from the maintenance vial and creating a 1:5 fold dilution in typical fashion. Initial dosing will start with one drop on day one, and increase by one drop each day until five drops are delivered on day five. Then the maintenance vial will be used, and the process will be started over until five drops are delivered on day five. At this point, a 0.2 mL daily maintenance dose will be administered using a needle-free TB type syringe. This dosing paradigm will be extrapolated to other antigens, as is commonly done with subcutaneous immunotherapy dosing paradigms. Further information can be obtained by attending one of the AAOA courses (Basic, Advanced, and Annual Meeting programs).

It should be understood that the AAOA is presenting a SLIT dosing schedule that is based on very limited information.

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JOINT ALLERGY & OTOLARYNGOLOGY SLIT WORKGROUP UPDATE

Last November, during the College meeting, we took the opportunity to create a unified workgroup with allergy and ENT to evaluate sublingual immunotherapy (SLIT) and define appropriate research, socioeconomic, and educational opportunities with the goal of maintaining our ability to deliver quality patient care.

As many of you are aware, SLIT is widely accepted through out Europe. Additionally, several US pharmaceutical and antigen companies are exploring opportunities to incorporate sublingual allergy management into the US treatment protocols.

With many third party interest groups evaluating the efficacy and marketplace for SLIT, it became apparent that the allergy and ENT communities needed to join forces to help evaluate these advances from the perspective of improving patient care. Working together we have a stronger voice and broader opportunities to influence the future delivery of allergy therapeutic care.

There has been much internal and external debate about dosing, billing, and overall impact related to SLIT. Our workgroup is focusing on these key issues—research: *what studies need to be undertaken to help identify dosing protocols?*; advocacy: *what are the appropriate billing and reimbursement mechanisms?, what are the risks associated with each, how do we develop billing protocols simultaneously with the development of dosing protocols?*; allergy incidence and therapeutic impact: *what do we need to consider as this technique evolves in terms of access to care and overall practice management concerns?* While there is no easy answer, we believe the answers will be uncovered if we evaluate all of these components concurrently.

CURRENT STATUS

SLIT CPT Code

At the present time, there is general agreement that we need more information to fully evaluate all the appropriate reimbursement options. We are evaluating is the risk and opportunity associated with each billing and reimbursement option, potential work values, and relative value units. We have agreed to identify studies necessary to support bringing a SLIT code request to the AMA CPT Committee should our evaluation dictate that this is the appropriate route. Currently, no widely agreed upon SLIT dosing protocol exists that is validated by well-designed clinical trials in the United States. Ideally, having a dosing protocol that is generally acceptable to all the allergy societies is important before we try to develop a CPT code proposal.

You should be aware that Medicare prohibits billing of 95165 for any other use than parenteral administration. Thus, if you are using 95165 for SLIT, and your patient's insurance has adopted Medicare rules (most carriers have done this), you should not bill 95165 for the cost of the extract, if it is administered sublingually. An informed consent document should state that currently SLIT is an off–label use of an approved product.

Antigen Studies

Single antigen studies need to be done to demonstrate safety and efficacy. After that demonstration is completed, we will need multiple antigen studies to allow for the broadest possible use of the SLIT product. In addition, there will be a need for further studies to define optimal dosing schedules (e.g., pre/co-seasonal, perennial, daily, every other day, etc). These will also help support the broadest use of SLIT—if it turns out to be effective for all of those uses. We do realize that we are now obligated to define efficacy beyond that currently defined for SCIT.

Off-label Use of Allergy Extract for SLIT

Many questions have arisen concerning the off-label use of allergy extract. You should be aware that "off-label prescribing—the prescription of a medication in a manner different from that approved by the FDA—is legal and common and is often done in the absence of adequate supporting data."[1] While the FDA currently does not allow manufacturers of a drug to advertise their off-label use, it has never exercised any authority over such use by physicians.

In conclusion, we are effectively working with our allergy and ENT colleagues to address many of the questions surrounding SLIT. This opportunity to collaborate will help assure we can continue to deliver quality care for our allergic patients. We will keep you posted on our progress.

[1] Stafford, Randal RS NEJM 358:14 April 3, 2008

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It is based on one single antigen study using antigens manufactured in the United States. This schedule is not a treatment guideline. As always physicians must use their own judgment in providing the best care for their patients.

[1] **Leatherman B**, Owen S, Chadwick S, et al. Sublingual Immunotherapy—Past, Present, Paradigm for the Future? A Review of the Literature. *Otolaryngology—Head and Neck Surgery*, 2007.136(3) supplement.

[2] Abstract presented at American Academy of Allergy, Asthma, and Immunology meeting.