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Oral Mucosal Immunotherapy Using a Toothpaste Delivery System for the Treatment of Allergic Rhinitis

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ABSTRACT Oral Mucosal Immunotherapy is a novel method of delivering allergenic extracts to the tolerogenic oropharyngeal mucosa using a compounded toothpaste vehicle. This article describes three cases where individuals with seasonal allergic rhinitis demonstrated symptom improvement as well as decreased skin reactivity after using Oral Mucosal Immunotherapy in a pre-seasonal and co-seasonal fashion.

Physicians worldwide who practice allergy are treating patients with allergic rhinitis (AR) using commercially available, concentrated, liquid allergenic extracts applied daily to the oral mucosa underneath the tongue (sublingual immunotherapy [SLIT]) over a 3- to 5-year period. However, this home therapy has poor long-term

adherence, which decreases its efficacy, and delivers extract to only a small portion of the oral cavity mucosa. In their 2013 position paper, the World Allergy Organization recognized the potential of the mucosal tissues in the oral vestibule and gingiva to induce an enhanced level of immune tolerance with decreased mast cell activation, and they

called for more work in this area.¹ In order to address these issues, our team has begun treating patients with AR using the same extracts which are compounded with a glycerin-based toothpaste delivery vehicle (oral mucosal immunotherapy [OMIT]). Three case reports using this compounded preparation are described in this article.

CASE REPORT #1

C.R. is a 42-year old female with a 25-year history of AR with sneezing, nasal itching, and rhinorrhea in the spring, along with perennial itching in the mouth when eating apples or raw vegetables. She has used oral antihistamines in the past, which have only partially controlled her symptoms. She underwent skin-prick testing (SPT) for tree pollens (Grade 0 to 4 based on the diameter of the wheal at 15 minutes), with positive reactions to oak (Grade 4), elm (Grade 3), cottonwood (Grade 3), birch (Grade 4), maple (Grade 3), and ash (Grade 4). She began OMIT in February 2012 by brushing once daily for 2 minutes with 1 mL of a toothpaste delivery vehicle compounded with 0.02 mL of oak and 0.02 mL of birch extract (Antigen Laboratories, Liberty, Missouri), delivering approximately 25 micrograms per day of each major antigen. In the first three days of treatment, she experienced a tingling sensation in the mouth without swelling, but experienced no adverse reactions for the remainder of the treatment, which continued until the end of May 2012. Allergy Outcome Survey (AOS) was completed at baseline (February), mid-season (April), and at the end of the season (June). She did not require any medications during the treatment period for symptom control, only reporting morning congestion and skin itching intermittently in May. She reported that she was able to peel carrots and potatoes without sneezing, which she had not been able to do before, and that her seasonal allergies were "alleviated by about 95% overall." Repeat SPT in June 2012 demonstrated an absence of skin reactivity to oak (Grade 0), while skin reactivity to birch and the other tree pollens remained unchanged.



SKIN PRICK TESTING

partial control of her symptoms. She also underwent SPT for tree pollens in February 2012 and tested positive for oak (Grade 4), elm (Grade 2), cottonwood (Grade 3), birch (Grade 4), maple (Grade 3), and ash (Grade 3). She was treated with OMIT toothpaste containing oak and birch extract from February 2012 to June 2012, and AOS was obtained as in Case #1. For the first week, she reported mild soreness in the gums, which resolved within 5 minutes after brushing. In March 2012, she reported for the first time that she could peel a potato without developing swelling on her hands. During April and May, she reported mild itchiness, sneezing, and morning nasal congestion, which were controlled with oral and nasal antihistamines as needed. She described her allergies as "a lot more mild than what they usually are this time of the year." Repeat SPT in June 2012 demonstrated a decrease of skin reactivity to oak from Grade 4 to Grade 3, while skin reactivity to birch and the other tree pollens remained unchanged.

CASE REPORT #2

N.R. is a 39-year old female with a life-long history of perennial AR with seasonal exacerbation, resulting in sneezing, nasal congestion, rhinorrhea, and itchiness in the nose and eyes. She also reported a history of asthma and swelling of her hands when peeling carrots or potatoes. She has used oral antihistamines, intranasal steroids, and leukotriene receptor antagonists with limited benefit and underwent a 4-year course of subcutaneous immunotherapy injections (SCIT) as a child, with only

CASE REPORT #3

B.R. is a 37-year old male with a history of seasonal AR with nasal congestion, rhinorrhea, and itchy eyes. Symptoms had previously been well controlled with oral antihistamines, but since he began working as a landscaper 5 years ago, he could no longer control his symptoms in the spring, despite using an intranasal spray containing both a steroid and an antihistamine. SPT in February 2012 was positive for oak (Grade 2) and birch (Grade 3), but negative (Grade 0) for elm, cottonwood, maple, and ash. He was also treated with OMIT toothpaste containing oak and birch extract from February 2012 to June 2012, and AOS was obtained as in Cases #1 and #2. He reported no adverse reactions when brushing with the OMIT toothpaste. He remained asymptomatic, even while on the job, until May, when he was able to use oral antihistamines and topic eye drops to control sneezing, itchy eyes, and sore throat. Repeat SPT in June 2012 demonstrated a complete absence of skin reactivity to oak but persistent skin reactivity to birch.

DISCUSSION

Approximately 20% to 40% of the U.S. population suffers from AR.² Currently, antigen-specific immunotherapy is the only disease-modifying treatment available for AR. Allergy extracts are delivered either via SCIT or SLIT on a consistent basis for approximately 3 to 5 years to achieve a long-term benefit. Since 1996, SLIT

has been recognized as a viable alternative to SCIT by the World Health Organization, and in a recent review by Lin et al, a moderate grade level of evidence was found to support the effectiveness of SLIT for both AR and asthma.^{3,4} In Europe, SLIT represents the majority of new immunotherapy prescriptions, and its use has also been steadily increasing in the U.S.⁵

The benefits of SLIT over SCIT include the convenience of home-based therapy, improved safety, and the ability to desensitize without the use of injections. However, adherence to SLIT is problematic, which limits both efficacy as well as the likelihood of completing therapy. Data from two large, Italian SLIT manufacturers demonstrated that fewer than 50% of patients renewed their SLIT prescription after the first year and nearly 90% had discontinued therapy by the third year.⁶ Other limitations to SLIT include the difficulty for some patients to place the correct amount of drops in the sublingual space, the leakage of liquid from the vial when traveling with it, and potential contamination of the vial from the dropper tip.

These three cases demonstrate the feasibility of a toothpaste vehicle to deliver antigen-specific extracts to the oral and sublingual mucosa in patients undergoing allergy immunotherapy. Successful desensitization is closely tied to therapy adherence, and by integrating this treatment into a universally-performed daily activity, it is expected that adherence will be optimized. A toothpaste formulation would also be advantageous during times of extended travel, such as during college or military deployment. Moreover, the exposure of extract to an extended population of oral Langerhans cells (oLC) might increase efficacy of the therapy or decrease the amount of extract required. Allam et al determined that oLC possess the high affinity receptor for IgE (FcεRI) and display natural pro-tolerogenic characteristics that are necessary for successful SLIT.⁷ Interestingly, the highest density of oLC in the oral cavity is in the vestibule, including the cheek and gingiva, while the lowest density is in the sublingual mucosa.⁸ The success of SLIT does not depend on absorption through the mucosa, but rather contact with oLC on the surface of the mucosa, and the competition for oLC created by the limited surface area in the sublingual space might explain the suggested decrease in efficacy when multiple antigens are placed in a SLIT vial.⁹ Finally, OMIT has the synergistic benefit of promoting good dental care, which has been linked to other health benefits such as decreased cardiac risk.¹⁰

The AOS generates a score from 0 (best) to 29 (worst) related to symptoms and medication use, as well as the perception of allergy severity compared to the previous year. The mean total scores of these three patients for February, April, and June were 3.0 ± 0.6 , 4.3 ± 3.4 and 7.0 ± 3.0 , respectively, which represents a statistically insignificant rise. The general rating of allergy symptoms compared to one year ago was “the same” in February, “much better” in April, and “somewhat better” in June. All three patients requested the same pre/co-seasonal treatment regimen with OMIT the following year. In 2013, the mean scores for February, April, and June were 3.3 ± 0.5 , 4.7 ± 1.2 and 5.7 ± 1.7 , respectively, again representing an insignificant rise in AOS. Comparison of AOS data with the same month in 2012 was “about the same” in February, “somewhat better” in April, and “much better” in June, right after the most severe month for spring allergies. Although a decrease in skin reactivity is not always seen, even after successful immunotherapy, this finding was a reliable indicator that desensitization had occurred. It is possible

that additional benefits may have occurred if additional tree extracts had been included in the OMIT toothpaste in case reports #1 and #2.

Because allergy extracts are in the 50% glycerin base, compounding it with toothpaste requires some special considerations. When combining the liquid extracts with commercially available toothpaste for these three patients, the compounder discovered that the result of the preparations was an undesirable paste consistency. In addition, the extracts would not combine with many of these preparations, or separated out within days of mixing. A glycerin-based toothpaste base of high viscosity appears to be optimal for OMIT, and the toothpaste base only becomes usable toothpaste when combined with the allergy extracts. The integrity of this toothpaste base is also believed to enhance the stability of the extract proteins by avoiding mechanical trauma produced by shearing forces from storage in liquid form.

When compounding the toothpaste base, care was taken to ensure optimal effects. The compounder allowed time for the ingre-

As simple as brushing your teeth

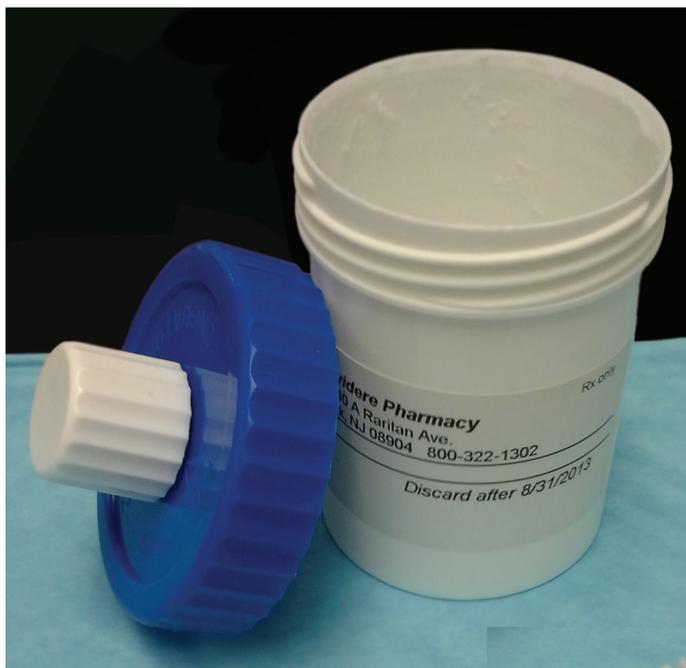
Allerdent™

Oral Mucosal Immunotherapy Toothpaste System

Specially formulated to incorporate and stabilize allergenic extracts

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dients to properly stir together, otherwise undesirable affects may have been experienced, such as bubbling, if the detergent was added too rapidly. Ideally, this should be made in a vacuum to reduce the risk of such adverse events. Also, to achieve the desired viscosity, several thickeners were added to the compound along with the necessary buffers, glycerin, and fluoride. To achieve the final deep white, opaque preparation, a pigment was added, along with a sweetener and flavoring (see Figure). Follow-up testing of the toothpaste base did not demonstrate any adverse interaction between the extract proteins and the other ingredients.

Personalizing this toothpaste likely plays a significant role in the success of OMIT, as in the case of the three patients discussed herein. Compounding allowed the physician to individualize each patient's treatment based on their personal allergens. After determining which allergens are the most clinically relevant for each patient, the physician can select specific extracts, with specific amounts, to be incorporated into the toothpaste simultaneously.

CONCLUSION

In summary, OMIT can be a viable option to treat patients with allergic rhinitis, particularly those who cannot, or will not, adhere to a weekly injection schedule, or those who have difficulty using daily SLIT drops. In the cases presented, results were evident after using the product for only 5 months. The toothpaste not only covers a larger mucosal surface area com-

pared to SLIT, with potentially enhanced effect, but the flavoring may also improve patient adherence. These three patients even requested to use the toothpaste the following year. These cases present enough evidence to support the necessity of further research to determine the stability of allergenic proteins in this specially-designed toothpaste base, and a clinical trial to study the effectiveness of OMIT, compared to existing immunotherapy delivery methods, for people with allergic disease.

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FIGURE.
High-viscosity toothpaste base.

Note: This glycerin toothpaste base has the smooth consistency of a commercial-grade, fluoride toothpaste once it is mixed with concentrated, liquid allergenic extracts.

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