

# Oral mucosal immunotherapy for allergic rhinitis: A pilot study

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## ABSTRACT

**Background:** The sublingual mucosa has been used for many years to apply allergenic extracts for the purpose of specific immunotherapy (IT). Although sublingual IT (SLIT) is both safe and efficacious, the density of antigen-presenting cells is higher in other regions of the oral cavity and vestibule, which make them a potentially desirable target for IT.

**Objective:** To present the concept of oral mucosal IT (OMIT) and to provide pilot data for this extended application of SLIT.

**Methods:** An open-label, 12-month, prospective study was undertaken as a preliminary step before a full-scale clinical investigation. Twenty-four individuals with allergic rhinitis received IT by applying allergenic extracts daily to either the oral vestibule plus oral cavity mucosa by using a glycerin-based toothpaste or to the sublingual mucosa by using 50% glycerin liquid drops. Adverse events, adherence rates, total combined scores, rhinoconjunctivitis quality-of-life questionnaire scores, changes in skin reactivity, and changes in serum antibody levels were measured for each participant.

**Results:** No severe adverse events occurred in either group. The adherence rate was 80% for the OMIT group and 62% for the SLIT group ( $p = 0.61$ ). Decreased total combined scores were demonstrated for both the OMIT group (15.6%) and the SLIT group (22.3%), although this decrease did not reach statistical significance in either group. Both groups achieved a meaningful clinical improvement of at least 0.5 points on rhinoconjunctivitis quality-of-life questionnaire. A statistically significant rise in specific immunoglobulin G4 (IgG4) was seen in both groups over the first 6 months of treatment.

**Conclusion:** OMIT and SLIT demonstrated similar safety profiles and adherence rates. Measurements of clinical efficacy improved for both groups, but only changes in IgG4 achieved statistical significance. These pilot data provide enough evidence to proceed with a full-scale investigation to explore the role of OMIT in the long-term management of allergic rhinitis.

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Approximately 20–40% of the U.S. population has allergic rhinitis (AR).<sup>1</sup> AR can have a significant impact on the quality of life of the individual and may also lead to further sensitization and the development of asthma.<sup>2,3</sup> Although AR is commonly treated with pharmacotherapy and environmental control strategies, antigen-specific immunotherapy (IT) is currently the only disease-modifying treatment available. Allergenic extracts are delivered either through subcutaneous injection (subcutaneous IT [SCIT]) or by application to the sublingual mucosa (sublingual IT [SLIT]) on

a consistent basis for ~3–5 years to achieve a long-term benefit.<sup>4</sup>

Since 1996, SLIT has been recognized as a potential alternative to SCIT by the World Health Organization, and the efficacy of the treatment for both AR and asthma has been confirmed in many randomized controlled trials and meta-analyses.<sup>5–7</sup> However, although the efficacy of both SCIT and SLIT versus placebo has been clearly demonstrated, conclusive head-to-head data are lacking.<sup>8</sup> One systematic review by Dretzke *et al.*<sup>9</sup> failed to demonstrate superiority of one delivery technique over another, whereas a separate systematic review concluded that there was moderate-grade evidence that favored SCIT for the reduction of AR symptoms.<sup>10</sup> In Europe, SLIT represents the majority of new IT prescriptions, and its use has also been increasing in the United States.<sup>11</sup>

Oral Langerhans cells (oLC) are antigen-presenting cells that possess the high affinity receptor for immunoglobulin E (IgE) and the natural protolerogenic characteristics that are necessary for successful IT.<sup>12</sup> Coupled with the production of interleukin 10 and transforming growth factor  $\beta$ , they are able to efficiently bind allergens and present them to T cells in local lymphoid tissue, which leads to an inhibitory effect on T-helper (Th) type 2-mediated (allergic) in-

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flammation.<sup>5,13</sup> Recently, it was discovered that the highest density of oLCs, and the most active expression of the high-affinity receptor, is in the vestibular and buccal regions of the oral cavity, whereas the lowest density is in the sublingual region.<sup>14</sup> In its 2013 position paper, the World Allergy Organization stated, "targeting the vestibule with allergen vaccine with or without adjuvant has the potential to induce enhanced immune deviation or tolerance, possibly with a lower potential for mast cell-related local side effects . . ." <sup>15</sup>

This pilot study was designed to assess the feasibility of a glycerin-based toothpaste vehicle for the delivery of allergenic extracts to the mucosa of the oral vestibule and oral cavity to desensitize individuals with AR (oral mucosal IT [OMIT]). The regions accessed by OMIT include the vestibular, buccal, lingual, gingival, palatal, and sublingual mucosa. Because of the anticipated difficulties in demonstrating statistically significant differences in this limited study population, the comparison group chosen would be receiving SLIT, an IT delivery method with known safety and efficacy. The primary hypothesis is that changes in medication scores, symptom scores, quality-of-life scores, skin reactivity, and serum antibody levels between OMIT and SLIT would be similar. Secondary hypotheses are that adverse events (AE) with OMIT would be limited to the oral cavity because the extract is not primarily swallowed and that adherence to therapy with OMIT might be higher than with SLIT.

## METHODS

### Study Population

Approval for this study was obtained from the institutional review board of Weill Cornell Medical College, New York City (protocol 1304013834). The study population consisted of adults ( $\geq 18$  years of age) with moderate-severe persistent AR who agreed to begin IT, based on a strong correlation between their sensitivities to airborne allergens and clinical symptoms, but declined SCIT. The goal was to enroll 12 individuals for the OMIT group and 12 individuals for the SLIT group. Sensitivities were determined through either skin-prick testing (SPT), intradermal testing, serum IgE analysis, or a combination of methods. A skin wheal diameter of  $>3$  mm at 15 minutes was considered positive. IgE levels of  $>0.35$  kU/L were considered positive for serum analysis. Pregnant individuals or those with a history of IT, either SCIT or SLIT, were excluded from participating in the study.

### Immunotherapy

Each individual was given the option to receive his or her daily dose of allergenic extract through either OMIT or SLIT. Before enrollment, informed consent was obtained from each individual after a discussion

that explained the risks, limitations, potential benefits, alternatives, and requirements of IT. Each of the 24 enrolled participants was given IT with the allergens relevant to their clinical history, as decided by the treating allergist (W.R.). The cost to each participant was the same for both groups,  $< \$100$  per month for the study period. SLIT vials and OMIT pumps were mixed by using commercially available, concentrated liquid extracts (Antigen Laboratories [Liberty, MO], Greer [Lenoir, NC], and Hollister-Stier [Spokane, WA]). Extracts from all suppliers were used in each group. For OMIT, the extracts were mixed with a commercial-grade, glycerin-based fluoride toothpaste, specifically formulated to incorporate allergenic extracts and maintain their stability for at least 12 months at room temperature (Belvidere Labs, Highland Park, NJ).

For each participant, the first dose was given in the office of the treating allergist (W. R. R.), with a 20-minute observation period to monitor for AEs and to ensure that he or she was administering the IT dose in the correct fashion. All subsequent doses were self-administered once daily by the participant from home. OMIT pumps were kept at room temperature, whereas participants were given the option to keep SLIT vials in or out of the refrigerator. The participants who received SLIT began therapy with a 10-day escalation period, by placing drops underneath the tongue and holding for 2 minutes before swallowing or expelling the liquid. No escalation schedule was used for OMIT, and the daily maintenance dose of extract was the same for both groups (0.02 mL of concentrated extract per allergen). The participants who received OMIT were instructed to place two pumps (0.9 mL) of toothpaste from a metered delivery system (TCD Inc., Lucedale, MS) onto their toothbrush and brush in standard fashion for 2 minutes without expelling the foam. After brushing, the participants were instructed to expel the residual foam and rinse with water if desired. The participants were instructed not to take their daily IT dose if they had a fever or felt poorly enough to miss work or school.

### Data Collection

Each participant was asked to complete a daily journal in which he or she entered information about his or her symptoms, medication use, successful administration of the daily IT dose, and any comments concerning AEs. Adherence to IT was defined as successful administration of at least 90% of doses in participants who completed 12 months of therapy. Doses missed due to illness or as directed by the supervising physician or allergy care provider were not counted as missed doses for the purpose of adherence determination.

The total combined score (TCS) was calculated by adding the symptom score and the medication score.<sup>16</sup>

Table 1 Group demographic characteristics

	OMIT (N = 12)	SLIT (N = 12)	p Value
Age, mean (range), y	33.9 (26–45)	34.9 (20–57)	0.93
Men, no (%)	6 (50)	6 (50)	1.0
Women, no. (%)	6 (50)	6 (50)	1.0
History of asthma, no. (%)	2 (16.7)	3 (25)	1.0
Allergens in treatment vial or pump, mean no. (range)	6.3 (3–0)	6.4 (4–9)	0.79

OMIT = oral mucosal immunotherapy; SLIT = sublingual immunotherapy.

The four symptoms that comprised the symptom score were nasal congestion, rhinorrhea, nasal itching, and sneezing (none, 0 points; mild, 1 point; moderate, 2 points; severe, 3 points). Two points each were assigned for each class of medication used for nasal symptoms on each day: antihistamines (oral, ocular, or intranasal), corticosteroids (oral or intranasal), decongestants (oral or intranasal) or any other class of medication (leukotriene receptor antagonist, intranasal anticholinergic spray, or mast cell stabilizer). The use of intranasal saline solution was not counted toward the medication score.

Quality of life was evaluated by using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).<sup>17</sup> The participants completed the RQLQ at the first visit before initiating either SLIT or OMIT and at the 12-month visit. Each item was rated on a scale of 0 to 6 (0, not troubled; 6, extremely troubled). The mean total RQLQ score was calculated by determining the mean of all 28 responses, and a decrease of 0.5 points was considered to represent a meaningful clinical improvement.

Each participant was scheduled for follow-up visits with the treating allergist every 3 months. During these visits, a physical examination was performed and information was gathered concerning their symptoms, medication use, AEs, and any difficulties they were having related to the treatment or study requirements. The toothpaste pumps or vials for the next 3 months were also provided during these visits. Those participants who had positive baseline SPT for the allergens in their treatment underwent SPT again at the 12-month visit for those allergens to assess changes in skin reactivity.

### IgE and IgG4 Measurements

Serum samples from all the participants were sent to a reference laboratory to determine total IgE (baseline and 12 months), specific IgE to all the treatment allergens (baseline and 12 months), and specific IgG4 to the treatment allergens (baseline, 6 months, 9 months, and 12 months) (PiRL, Portage, MI).

### Statistical Analysis

Data are presented as mean (standard deviation [SD]) values. Fisher exact probability testing was used

to compare categorical clinical variables between the groups, including age, sex, asthma prevalence, mean number of treatment allergens, AEs, adherence rates, and changes in skin reactivity. Comparisons of continuous clinical variables between the groups, including TCS, RQLQ scores, and antibody levels were performed by using the nonparametric Mann-Whitney *U* test and the Kruskal-Wallis test. Two-tailed *p* values were calculated by using VassarStats online statistical software (Vassar College, Poughkeepsie, NY), and a value of *p* < 0.05 was considered statistically significant.<sup>18</sup>

## RESULTS

### Study Population

The demographic characteristics of the 24 study participants are presented in Table 1. A total of 14 participants (58%) were diagnosed by using skin testing alone (6 OMIT, 8 SLIT), whereas 5 participants (21%) were diagnosed by using serum IgE analysis (3 OMIT, 2 SLIT) and 5 participants (21%) were diagnosed with a combination of skin testing and serum IgE analysis (3 OMIT, 2 SLIT).

As demonstrated in Table 2, there was no significant difference in the distribution of allergens in the treatments between the OMIT and SLIT groups. For the OMIT group, the allergens used for treatment were *Alternaria*, American elm, *Aspergillus*, cat, cockroach, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, dog, ragweed, red birch, red maple, timothy grass, white ash, and white oak. For the SLIT group, the allergens used for treatment were *Alternaria*, *Candida*, cat, cockroach, *D. farinae*, *D. pteronyssinus*, dog, *Fusarium*, ragweed, red birch, red maple, rough pigweed, timothy grass, white ash, and white oak.

The dropout rates were 2 of 12 (16.7%) for the OMIT group and 4 of 12 (33.3%) for the SLIT group (*p* = 0.64). For the OMIT group, one of the two participants dropped out for unknown reasons before the 3-month visit and could not be contacted, whereas the other participant dropped out during the 3–6-month period because of financial difficulties. For the SLIT group, all four participants who dropped out did so during the 3–6-month period, three for medical reasons and one

Table 2 Number (%) of participants who received each allergen by group

Allergen (concentration)	OMIT (N = 12)	SLIT (N = 12)	p Value
<i>Alternaria</i> (1:20 w/v)	4 (33.3)	2 (16.7)	0.64
American elm (1:20 w/v)	2 (16.7)	0 (0)	0.48
<i>Aspergillus</i> (1:20 w/v)	1 (8.3)	0 (0)	1.0
<i>Candida</i> (1:20 w/v)	0 (0)	1 (8.3)	1.0
Cat (10,000 BAU/mL)	11 (91.7)	9 (75)	0.59
Cockroach (1:20 w/v)	4 (33.3)	6 (50)	0.68
<i>Dermatophagoides farinae</i> (10,000 AU/mL)	10 (83.3)	11 (91.7)	1.0
<i>Dermatophagoides pteronyssinus</i> (10,000 AU/ml)	9 (75)	11 (91.7)	0.59
Dog (1:20 w/v)	4 (33.3)	3 (25)	1.0
<i>Fusarium</i> (1:20 w/v)	0 (0)	1 (8.3)	1.0
Ragweed (1:20 w/v)	4 (33.3)	4 (33.3)	1.0
Red birch (1:20 w/v)	7 (58.3)	7 (58.3)	1.0
Red maple (1:20 w/v)	6 (50)	2 (16.7)	0.19
Rough pigweed (1:20 w/v)	0 (0)	1 (8.3)	1.0
Timothy grass (10,000 BAU/mL)	7 (58.3)	8 (66.7)	1.0
White ash (1:20 w/v)	2 (16.7)	4 (33.3)	0.64
White oak (1:20 w/v)	4 (33.3)	7 (58.3)	0.41
Total	75	77	

OMIT = oral mucosal immunotherapy; SLIT = sublingual immunotherapy.

Table 3 Number (%) of adverse events by group and category

Adverse Event	Total (N = 24)	OMIT (N = 12)	SLIT (N = 12)	p Value
Oral cavity	16 (66.7)	10 (83.3)	6 (50)	0.19
Skin	3 (12.5)	1 (8.3)	2 (16.7)	1.0
Gastrointestinal	2 (8.3)	0 (0)	2 (16.7)	0.48
Upper respiratory system and/or eye	1 (4.2)	0 (0)	1 (8.3)	1.0
Lower airway	0 (0)	0 (0)	0 (0)	1.0
Anaphylaxis and/or cardiovascular	0 (0)	0 (0)	0 (0)	1.0

OMIT = oral mucosal immunotherapy; SLIT = sublingual immunotherapy.

for unknown reasons. None of the participants in either group dropped out because of AEs related to their IT treatment.

### AEs

AEs for both the OMIT and SLIT groups are presented in Table 3. Eleven AEs were documented for each group. Overall, there was no significant difference in either the total AEs or the individual AE incidence between the two groups. The most common AEs for each group were itching, tingling, or swelling in the oral cavity. All of these events were mild, transient, and generally limited to the first week of therapy. Skin reactions included pruritus of the hands, arms, scalp, and ears. Gastrointestinal events in the SLIT group included worsening reflux and itching in the throat when the drops were swallowed. One participant in the SLIT group experienced an episode of increased nasal congestion after drop application. None of the

AEs resulted in missed doses, and no lower airway or cardiovascular events were noted during the study period for either group.

### Adherence to Therapy

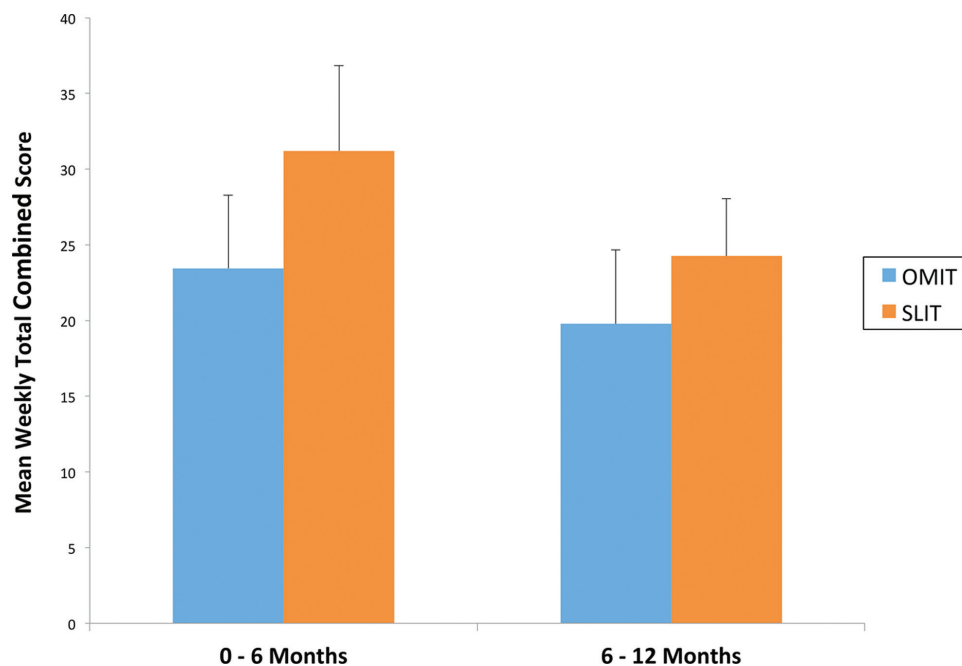
Successful adherence to therapy was seen in 8 of 10 participants (80%) in the OMIT group and in 5 of 8 participants (62%) in the SLIT group ( $p = 0.61$ ). Of the adherent participants in the OMIT group, the mean (SD) number of missed daily doses was  $4.75 \pm 7.03$ , whereas the adherent participants in the SLIT group missed  $10.40 \pm 8.53$  doses ( $p = 0.14$ ).

### TCS

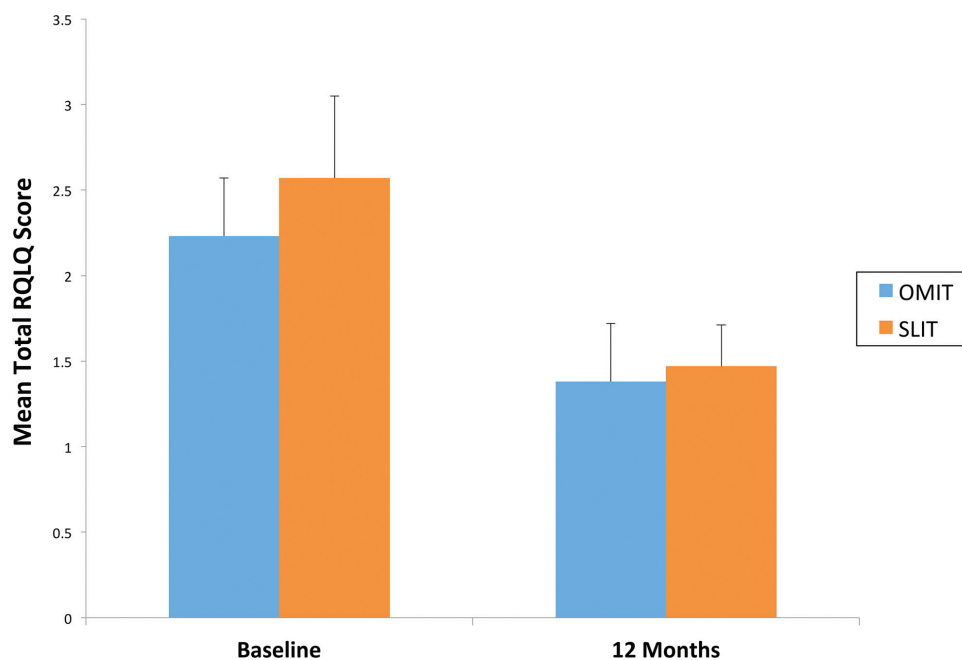
The mean weekly TCS for each group during the 0–6-month and 6–12-month periods was calculated, and the results are shown in Fig. 1. A decrease in the mean weekly TCS was noted for both the OMIT group



**Figure 1.** Mann-Whitney U test, comparing the improvement in mean weekly total combined scores (TCS) between the oral mucosal immunotherapy (OMIT) and sublingual immunotherapy (SLIT) groups during the first 6 months of therapy and the last 6 months of therapy. Mean  $\pm$  standard error. There was no significant difference between OMIT and SLIT groups at 0–6 months ( $p = 0.27$ ) or at 6–12 months ( $p = 0.54$ ). There was a nonsignificant decrease in TCS from 0–6 months to 6–12 months for both the OMIT group ( $p = 0.52$ ) and the SLIT group ( $p = 0.56$ ).



**Figure 2.** Mann-Whitney U test, comparing the improvement in mean total Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores between the oral mucosal immunotherapy (OMIT) and sublingual immunotherapy (SLIT) groups at baseline and after 12 months of therapy. Mean  $\pm$  standard error. There was no significant difference between OMIT and SLIT groups at baseline ( $p = 0.62$ ) or 12 months ( $p = 0.69$ ). There was a nonsignificant decrease in RQLQ scores between baseline and 12 months for both the OMIT group ( $p = 0.06$ ) and the SLIT group ( $p = 0.10$ ).

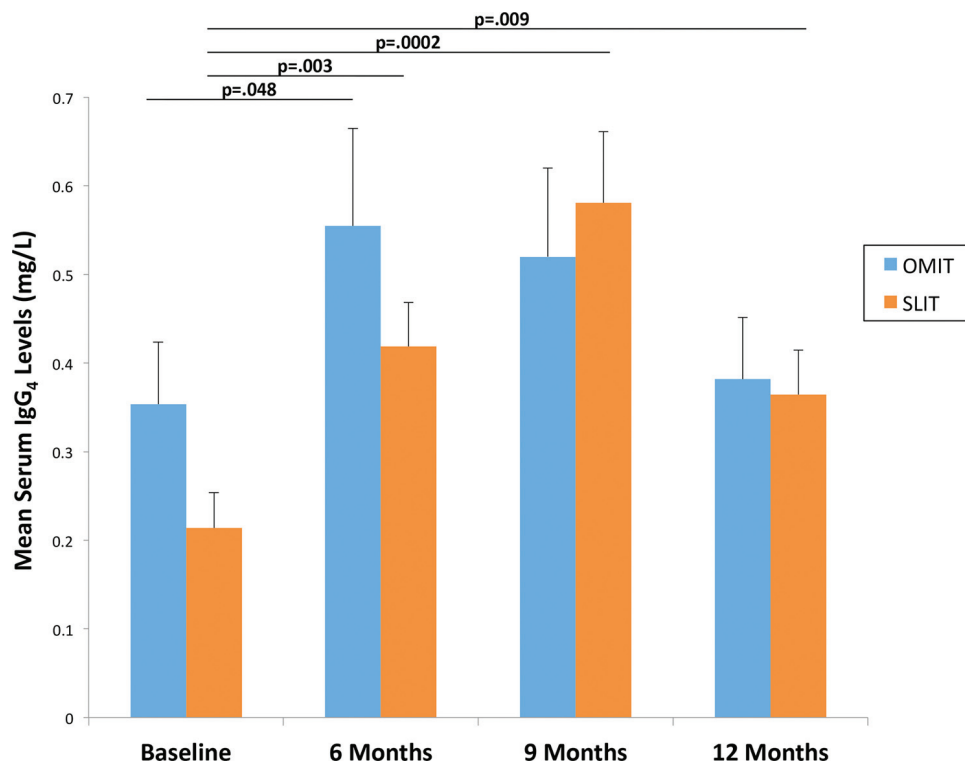


(15.6%) and the SLIT group (22.3%). In the OMIT group, the mean (SD) weekly TCS was  $23.45 \pm 15.32$  during the 0–6-month period and  $19.79 \pm 15.39$  during the 6–12-month period ( $p = 0.52$ ). In the SLIT group, the mean (SD) weekly TCS was  $31.21 \pm 15.96$  during the 0–6-month period and  $24.26 \pm 10.69$  during the 6–12-month period ( $p = 0.56$ ). No significant differences were noted in mean weekly TCS between the OMIT and SLIT groups during the 0–6-month period ( $p = 0.27$ ) or the 6–12-month period ( $p = 0.54$ ). One participant in the OMIT group used a 1-week course of oral steroids during the first 6 months of therapy after a period of high allergen exposure; one

participant in the SLIT group received 2 weeks of oral steroids during the first 6 months of therapy for symptoms associated with acute sinusitis.

### Quality-of-Life Scores

The mean total RQLQ score for each group at baseline and 12 months was calculated, and the results are presented in Fig. 2. A meaningful clinical improvement was demonstrated for both groups. In the OMIT group, the mean (SD) total RQLQ score was  $2.23 \pm 1.09$  at baseline and  $1.38 \pm 1.06$  at 12 months ( $p = 0.06$ ). In the SLIT group, the mean (SD) total RQLQ score was



**Figure 3.** The Kruskal-Wallis test with pairwise comparisons of the change in mean serum immunoglobulin G4 (IgG4) levels over time for the oral mucosal immunotherapy (OMIT) and sublingual immunotherapy (SLIT) groups. Mean  $\pm$  standard error. Statistically significant differences ( $p < 0.05$ ) are indicated on the graph above. There was no significant difference between OMIT and SLIT groups at baseline ( $p = 0.26$ ), 6 months ( $p = 0.98$ ), 9 months ( $p = 0.27$ ), or 12 months ( $p = 0.42$ ). There was no significant difference between baseline and 9 months ( $p = 0.13$ ) and between baseline and 12 months ( $p = 0.81$ ) for the OMIT group.

$2.57 \pm 1.36$  at baseline and  $1.47 \pm 0.68$  at 12 months ( $p = 0.10$ ). No significant differences were noted in mean total RQLQ score between the OMIT and SLIT groups at baseline ( $p = 0.62$ ) or at 12 months ( $p = 0.69$ ).

### Changes in Skin Reactivity

Among the six participants diagnosed who used SPT in the OMIT group, 16 of 37 allergens (43.2%) demonstrated a decrease in wheal diameter. In comparison, among the 7 participants diagnosed who used SPT in the SLIT group, 14 of 33 allergens (42.4%) demonstrated a decrease in wheal diameter ( $p = 1.0$ ).

### IgE and IgG4 Levels

There were no significant differences in the total IgE levels between the groups at baseline ( $p = 0.83$ ) or at 12 months ( $p = 0.50$ ), but the overall specific IgE levels for the treatment allergens for both groups increased. There were no significant differences in the mean (SD) specific IgE levels between the groups at baseline ( $p = 0.70$ ) or at 12 months ( $p = 0.33$ ). For the OMIT group, specific IgE levels increased from  $7.54 \pm 13.93$  kU/L at baseline to  $12.13 \pm 22.99$  kU/L at 12 months ( $p = 0.57$ ). In the SLIT group, mean (SD) specific IgE levels increased from  $7.37 \pm 13.27$  kU/L at baseline to  $17.06 \pm 27.54$  kU/L at 12 months ( $p = 0.09$ ).

In both the OMIT and SLIT groups, there was a statistically significant rise in overall specific IgG4 levels from baseline to 6 months ( $p = 0.048$  and  $p = 0.003$ , respectively) (Fig. 3). In the OMIT group, increased IgG4 levels were seen in 8 of 14 treatment allergens

(57%), whereas increased IgG4 levels were seen in 12 of 14 treatment allergens (86%) in the SLIT group. For the allergens in the OMIT group associated with a rise in IgG4, peak levels were achieved by the 6-month visit for seven of eight allergens (87.5%), whereas peak levels were achieved by the 9-month visit for one of eight allergens (12.5%). For the allergens in the SLIT group associated with a rise in IgG4, peak levels were achieved by the 6-month visit for 2 of 12 allergens (16.7%), whereas peak levels were achieved by the 9-month visit for the remaining 10 of 12 allergens (83.3%).

### DISCUSSION

Located at a privileged access point in the body, the oral mucosal epithelium is particularly well adapted to process foreign allergens, ignoring those not perceived to be a threat while transferring others to deeper layers of immune tissue when necessary. The high level of oLCs, combined with the paucity of eosinophils and mast cells, makes the oral mucosal epithelium, particularly the vestibule, a potentially ideal location for IT.<sup>19</sup> Previously, a published case series indicated that there was a benefit from pre- and coseasonal OMIT based on decreased skin reactivity and improvements in Allergy Outcome Survey scores, in three individuals with seasonal AR who were sensitive to birch and oak pollen.<sup>20</sup>

OMIT expands the area of contact with allergenic extract proteins beyond the sublingual mucosa into the immunologically active mucosa of the oral vestibule and oral cavity. Allam *et al.*<sup>21</sup> reported that oLCs from

this region are able to take up timothy grass allergen (Phl p 5) within 5 minutes of exposure, which resulted in the production of inhibitory cytokines and attenuated cell maturation. Once allergenic proteins are taken up by oLCs, they remain bound for up to 20 hours.<sup>22</sup> Theoretically, the distribution of extract to a wider population of oLCs could limit the competition of extract proteins for binding sites, thus reducing the amount of unbound proteins.

As noted previously, the highest density of oLCs are in the vestibular and buccal mucosa, but they are also present in the gingival, lingual, palatal, and sublingual mucosa.<sup>14</sup> The application of extract through brushing removes debris and surface epithelial tissue, which potentially exposes deeper populations of oLCs. Moreover, it was determined that repeated disruption of the epithelial surface, even without the presence of allergenic proteins, helps drive the T-cell population from a proallergic, Th2-dominated phenotype toward a more normal, Th1-dominated immune response.<sup>23</sup> Further investigation will be required to determine whether this technique of allergen delivery in the oral cavity has a greater impact on the efficacy of IT or whether it allows for equivalent efficacy at lower extract doses.

OMIT offers a potential advantage by linking therapy to a universally performed daily activity. It is often difficult for IT users, particularly children, to hold liquid extracts under their tongue for 2 minutes or to judge how many drops have been deposited in the sublingual space. Poor adherence, either in the form of missed doses or inaccurate doses, has ramifications on both efficacy and the likelihood of completing the necessary 3–5 years of therapy. Analysis of data from two large, Italian SLIT manufacturers reported that <50% of patients renewed their SLIT prescription after the first year and nearly 90% had discontinued therapy by the third year.<sup>24</sup> In a real-life study on persistence for SLIT in The Netherlands, only 18% of users reached the minimally required treatment period of 3 years, with a median therapy duration of 0.6 years.<sup>25</sup> In a follow-up study of 40 individuals desensitized to peanut with SLIT, by using liquid extract, >50% discontinued their therapy over a period of 2–3 years, mostly for reasons other than AEs.<sup>26</sup>

The safety of SLIT has been clearly demonstrated. A recent Cochrane meta-analysis reported that most AEs were limited to the oral cavity and were mild to moderate in severity.<sup>6</sup> The same was true for both groups in this study, with most oral cavity AEs resolving within 1–2 weeks. No cardiovascular reactions were noted for either group, which reduced the concern that allergenic proteins might enter the intravascular space, particularly after brushing. Gastrointestinal AEs were only noted in the SLIT group, perhaps because the majority of the participants swallowed their drops. A recent meta-analysis by Lucendo *et al.*<sup>27</sup> indicated a positive

association among oral IT, use of swallowed food allergens, and the development or exacerbation of eosinophilic esophagitis. However, reports of eosinophilic esophagitis associated with pollen SLIT (both with liquid drops and with tablets) have also been documented, which indicates that expelling extracts, whenever possible, may have a safety benefit over swallowing them.<sup>28,29</sup>

It is known that IgE and IgG4 increase during the early phase of IT, more dramatically with SCIT than with SLIT.<sup>30</sup> Results of studies have also demonstrated that these changes do not consistently occur and do not correlate with clinical benefit.<sup>31,32</sup> It has been indicated that the rise in IgG4 is simply a marker of inflammation when foreign proteins enter the body, particularly when they are injected into subcutaneous tissues.<sup>33</sup> For both groups, IgG4 rose significantly over a 6–9-month period before declining by the 12-month visit.

The main limitation to this study was the small study population, a problem inherent to many pilot studies. The measurements and comparisons made were not intended to demonstrate the superiority of one IT strategy over another but rather to collect enough information about the feasibility of OMIT to determine whether or not a full-scale investigation would be warranted. During the planning of this study, it was anticipated that statistically significant changes would be difficult to demonstrate. Nonetheless, analysis of these data strongly indicated that the extract proteins in both groups established contact with oLCs and produced a measurable response from the immune system with a reasonable level of safety, which thus fulfilled the goal of this study.

## CONCLUSION

This “real-world” study demonstrated that OMIT, a new method for delivering allergenic extracts to the oral vestibule and oral cavity mucosa, produced similar changes in symptom and medication scores, quality-of-life scores, skin reactivity, and antibody levels compared with liquid SLIT in individuals with AR. There were no statistically significant differences in terms of AEs, clinical efficacy, or biologic response between the two methods of IT evaluated. Adherence seemed favorable in the OMIT group, but further investigation will be required to explore that hypothesis. When taking these findings into account, there is enough justification to proceed with full-scale, placebo-controlled studies, including both adults and children, to clarify the long-term efficacy, optimal dosing, and safety profile for OMIT.

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