Brief report

Real-world safety and effectiveness analysis of low-dose preschool sesame oral immunotherapy

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Background: Previous studies support the effectiveness of sesame oral immunotherapy (S-OIT) in patients >4 years old using maintenance doses of 1200 mg protein. However, tahini is often not palatable to children, and high-maintenance doses may not be possible for preschoolers.

Objective: We studied the safety and effectiveness outcomes of preschoolers with sesame allergy who underwent low-dose S-OIT of 200 mg protein.

Methods: Preschoolers with sesame allergy, with a history of objective reaction to sesame, and with either a positive skin prick test result (wheal diameter ≥3 mm) or sesame-specific IgE level ≥0.35 kU/L were included. Doses were escalated every 2 to 4 weeks until the maintenance dose of 200 mg of sesame protein was reached. The maintenance dose was continued daily for 1 year, followed by exit oral food challenge (OFC). Primary safety outcomes included allergic reactions grade 2 or higher and the need for epinephrine therapy during buildup. The primary effectiveness outcome was proportion of patients tolerating a minimum of 2000 mg sesame protein at exit OFC.

Results: Twenty-eight preschoolers (median age, 33.5 months) were enrolled to receive S-OIT. During the buildup phase, 9 subjects (32.1%) had no reaction, and 8 (28.6%) and 11 (39.3%) had grade 1 and 2 reactions, respectively. One patient (3.57%) received epinephrine for a grade 2 reaction. Twenty-one (91.3%) of 23 eligible subjects underwent exit OFC; 18 (85.7%) of these 21 patients successfully completed exit OFC. One (4.8%) and 2 (9.5%) subjects had grade 1 and 2 reactions, respectively, during OFC.

Conclusions: A lower and age-appropriate maintenance dose is safe and effective in desensitizing preschoolers with sesame allergy. (J Allergy Clin Immunol Global 2024;3:100171.)

Key words: *Sesame, oral immunotherapy, low dose, preschoolers, allergy*

INTRODUCTION

Evidence from Israel supports the effectiveness of sesame oral immunotherapy (S-OIT) in patients older than 4 years, with a daily maintenance dose provided of 1200 mg protein (5 g tahini).[1] After more than 6 months of maintenance therapy, 88.4% and 78.3% experienced desensitization to 1000 and 4000 mg sesame protein, respectively.[1] However, tahini is often not palatable to children, and high-maintenance doses may not be attainable by preschoolers. In this study, we present the safety and effectiveness outcomes of Canadian preschoolers with sesame allergy who underwent low-dose S-OIT using a 200 mg protein maintenance dose in a real-world setting.

Preschoolers (9-70 months old) with sesame allergy were enrolled onto the Food Allergy Immunotherapy registry from community and academic allergy clinics across Canada. Patients were included if they had an objective reaction to sesame before initiating OIT, and either a positive skin prick test (SPT) result (wheal diameter ≥3 mm) using standard reagent (ALK-Abelló, Horsholm, Denmark) or sesame-specific IgE (sIgE) level ≥0.35 kU/L. Patients undergoing multiple food OIT that included sesame were excluded. Dose escalations were performed every 2 to 4 weeks at the discretion of the treating physician until the maintenance dose of 200 mg sesame protein was reached (Table I). A dose of 200 mg was chosen for ease of measurement (1 mL tahini) and taste considerations. Adverse reactions during S-OIT were graded and managed according to a previously published flowchart.[2,3] SPT and sIgE were performed at baseline and selectively at maintenance or before oral food challenges (OFCs) at the discretion of the treating physician.

After approximately 1 year of maintenance therapy, patients underwent exit OFC, targeting a minimum cumulative dose of 2000 mg sesame protein using tahini. Primary safety outcomes for this study included an allergic reaction of grade 2 or higher[4] and epinephrine therapy during S-OIT buildup. The primary effectiveness outcome was the proportion of patients tolerating a minimum cumulative dose of 2000 mg sesame protein at exit OFC after approximately 1 year of daily maintenance treatment. The

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Abbreviations used
OFC: Oral food challenge
OIT: Oral immunotherapy
sIgE: Specific IgE
S-OIT: Sesame OIT
SPT: Skin prick test

2000 mg dose was chosen because it was considered to better represent a serving size for a preschool-age group based on taste (ie, 2000 mg is equivalent to the sesame protein content of 90 mL [4 tablespoons] of hummus). If the subject could consume beyond 2000 mg sesame protein, the OFC was continued up to a maximum dose of 4000 mg sesame protein.

Descriptive statistics were compiled for all variables. Data were analyzed by Stata 15 (StataCorp, College Station, Tex). This study was approved by the University of British Columbia/British Columbia Children's Hospital research ethics board.

TABLE I. Protocol for sesame OIT with 200 mg maintenance dose

Visit no.	Food protein (mg)	Absolute quantity of food measured*
1†	3	7 mg sesame flour
2	6	15 mg sesame flour
3	12	30 mg sesame flour
4	25	62 mg sesame flour
5	50	124 mg sesame flour
6	80	0.4 mL tahini
7	120	0.6 mL tahini
8	160	0.8 mL tahini
9	200	1 mL tahini

Exact allergen content may vary according to brand; it is crucial to confirm dose calculations of protein content for brand or form of food before providing dosing suggestions. Dose increases are performed every 2-4 weeks using this protocol.
*Sesame flour (Kevela Organic Sesame Flour, Dallas, Tex) contained 40.32 g sesame protein per 100 g sesame flour. Tahini (Organic Fair Trade Sesame Tahini, Nuts to You Nut Butter, Brantford, Ontario, Canada) contained 200 mg sesame protein/mL tahini.
†Optional.

RESULTS AND DISCUSSION

Between January 2019 and April 2022, a total of 28 preschoolers with a median age of 35.5 months (interquartile range, 23.3-41.8) were enrolled onto S-OIT. Of these, 2 children (7.14%) dropped out, 1 during the buildup because the subject disliked the taste of tahini, and 1 after completing exit OFC because of the burden of doing daily home dosing (Fig 1). Baseline characteristics, safety, and effectiveness outcomes are summarized in Table II. During the buildup phase, 9 subjects (32.1%) had no reaction, and 8 (28.6%) and 11 (39.3%) had grade 1 and 2 reactions, respectively. One patient (3.57%) received epinephrine for a grade 2 reaction during buildup. None required epinephrine during maintenance, and none developed symptoms suggesting eosinophilic esophagitis.

After 1 year of maintenance treatment, 21 of 23 eligible subjects underwent exit OFC. Eighteen of 21 subjects successfully exited, demonstrating an 85.7% effectiveness. Three (14.3%) developed reactions during the OFC, 1 (4.8%) grade 1 reaction and 2 (9.5%) grade 2 reactions (Table II). Subject 1 initiated S-OIT at 57 months, with an initial reaction before OIT of urticaria and angioedema at 9 months. The baseline SPT and sIgE were 12 mm and 4.87 kU/L, respectively. After 1 year of maintenance S-OIT, the SPT and sIgE were 4 mm and 18.2 kU/L, respectively. During exit OFC, the patient developed a mild grade 2 reaction with angioedema and conjunctivitis after a cumulative dose of 1000 mg of protein. Symptoms were not considered to require epinephrine and were managed with a nonsedating antihistamine. The patient returned for a second OFC 1 year later and tolerated 1700 mg of protein. Subjects 2 and 3 didn't mind the taste of tahini, so the families were interested in challenging to >2000 mg protein. Subject 2 started S-OIT at 32 months with an initial reaction before OIT of urticaria at 8 months. The baseline SPT and sIgE were 5 mm and 1.0 kU/L, respectively, and repeat sIgE before exit OFC was 1.17 kU/L. The patient had a grade 1 reaction with itchy throat after 4000 mg of protein. Subject 3 started S-OIT at 37 months with an initial reaction before OIT of urticaria at 6 months. The baseline SPT and sIgE were 6 mm and 2.37 kU/L, respectively. The patient developed a mild grade 2 reaction consisting of isolated abdominal pain after a cumulative dose of 2800 mg of sesame protein. No subjects developed symptoms suggestive of eosinophilic esophagitis throughout the study.

To our knowledge, this is the first real-world S-OIT study demonstrating that a lower maintenance dose of 200 mg of sesame protein is safe and effective in preschoolers. Our results suggest that the peanut OIT protocol developed by our Canadian Preschooler Peanut Oral Immunotherapy Therapy (CPP-OIT) collaboration may be safely extrapolated to sesame allergy in preschoolers, with similar effectiveness.[3,5] Compared to the previous study conducted in Israel,1 participants in our study were younger (median age, 35.5 vs 90 months), had fewer grade 2 reactions (39.3% vs 48.8%) during buildup, and required less epinephrine during the buildup (3.57% vs 16.7%) and maintenance (0 vs 8.3%) phases. One likely reason for the lower proportion of reactions in our study compared to the Israeli study is the age difference (median age, 33.5 vs 90 months),[1] as previously shown in peanut OIT studies.[6] Another possible explanation could be the use of a significantly lower maintenance dose (200 vs 1200 mg). Notably, prior research has demonstrated that a lower OIT maintenance dose improves adherence and reduces the risk of adverse reactions.[7] Additionally, the low-dose S-OIT protocols used in this study may be more suitable for younger children and infants, therefore facilitating the implementation of S-OIT by parents and improving tolerance. (The worse taste of tahini compared to peanut made 200 mg protein more acceptable than 300 mg.)

This study has some limitations. Similar to previous studies by our group, baseline OFCs were not mandatory in this study.[3,5,8] However, this is reflective of real-world practice, in which an OFC is not essential when there is a convincing objective reaction with a positive SPT or sesame sIgE. An additional limitation is the potential for spontaneous resolution of sesame allergy. A recent study by Mahlab-Guri et al studied 190 children with sesame allergy and reported a spontaneous resolution rate of 32.1% at a mean age of 3.54 years.[9] The authors reported that a milder initial reaction, younger age at diagnosis, smaller SPT (<7 mm), and a lack of concomitant tree nut allergy were predictors of spontaneous resolution.[9] However, sesame allergy persisted in 63.6% of patients with initial grade 1 reactions, 57.6% of patients with sesame allergy onset <10 months, and 58.6% with initial SPT

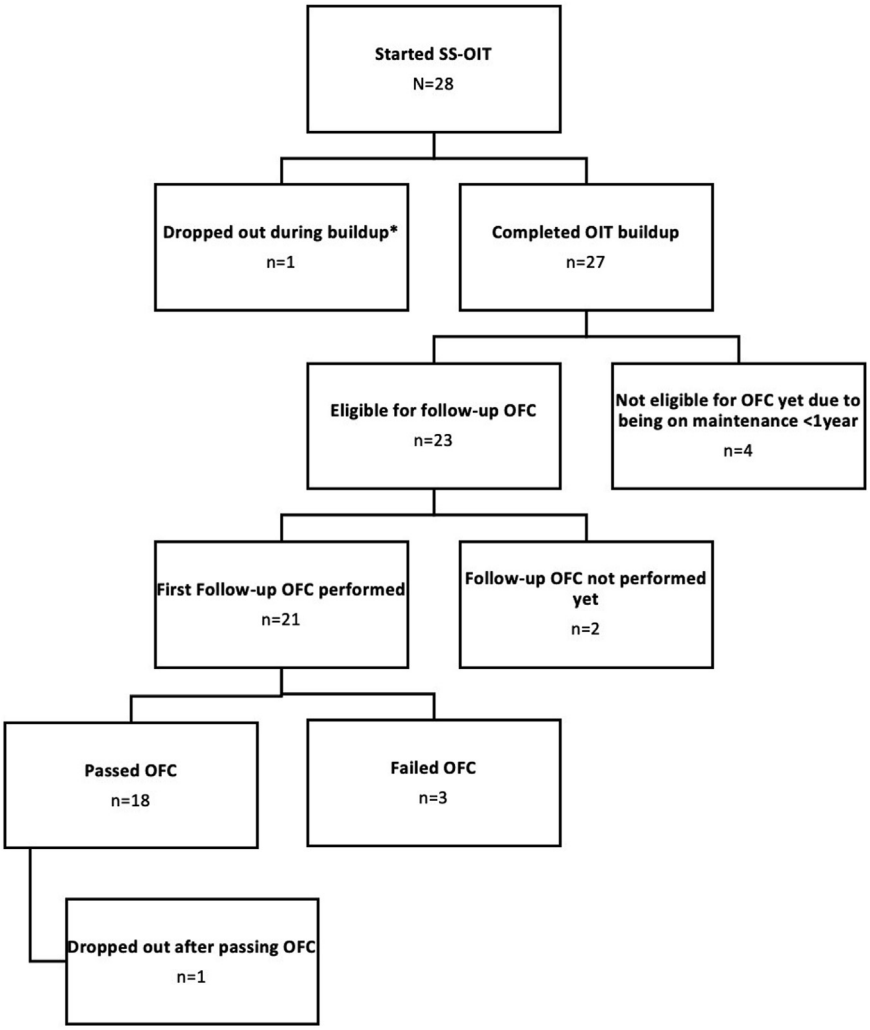

FIG 1. Flow diagram of preschoolers with sesame allergy enrolled in Canadian Food Allergy Immunotherapy program included in analysis. *Reasons for dropping out during buildup and after exit OFC were: 1 subject disliked tahini's taste; 1 found daily home dosing burdensome.

<7 mm, thereby making it challenging to predict who will experience spontaneous resolution. Additionally, the median SPT wheal size was 8 mm among our patients, which was identified as a risk factor for persistent sesame allergy, further supporting the potential need for S-OIT.[9]

Eighteen of the 21 subjects who underwent exit OFC passed. The choice of 2000 mg sesame protein as the minimum target cumulative dose for exit OFC is lower than the previously studied dose of 4000 mg protein for peanut. The 2000 mg dose was chosen to increase acceptability of the OFC because it was thought to better represent a typical serving size for this age group (ie, 2000 mg is equivalent to the sesame protein content of 90 mL of hummus) based on taste. Baumert et al demonstrated that increasing the reaction threshold from ≤100 to 300 mg peanut protein before and after peanut OIT, respectively, reduces the risk of an allergic reaction by >95% for accidental exposure to food products containing traces of peanut residue; and increasing the reaction threshold to 1000 mg peanut protein would have an additional quantitative benefit in reducing the risk for patients who reacted to ≤300 mg at baseline.[10] It is reasonable to use 2000 mg sesame protein as the exit OFC dose because all patients could be declared safe not only against accidental sesame exposure but also from an age-appropriate serving of sesame. There was a slightly lower dropout rate (7.14%) in this study compared to our previously published peanut OIT study, which had a dropout rate of around 10%.[3,5] One of the 2 subjects discontinued S-OIT because the sesame products were unpalatable, highlighting the practical importance of exploring the safety and effectiveness of low-dose S-OIT, as well as using other sesame products for S-OIT. These subjects are advised to continue with regular sesame consumption after passing exit OFC and sustained unresponsiveness was not evaluated.

In summary, our study provides preliminary evidence that a lower and age-appropriate maintenance dose is safe and effective in desensitizing preschoolers with sesame allergy.

DISCLOSURE STATEMENT

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TABLE II. Baseline characteristics and safety and effectiveness outcomes for sesame OIT in 28 preschoolers

Characteristic	Value
Age (months) at OIT initiation, median (IQR)	33.5 (23.3, 41.8)
Male sex	13 (46.4)
Other atopic conditions	
Eczema	16 (57.1)
Asthma	3 (10.7)
Allergic rhinitis	1 (3.57)
Other food allergies*	
Egg	8 (28.6)
Cow's milk	4 (14.3)
Peanut	9 (32.1)
Tree nut	7 (25.0)
Age (months) at initial reaction, median (IQR)	10.5 (8, 15.3)
Grade of initial reaction	
Grade 1	23 (82.1)
Grade 2	5 (17.9)
Grade 3	0
Grade 4	0
Baseline sesame SPT, median (IQR)	8 (6, 10)
Baseline sesame sIgE, median (IQR)	3.7 (1.53, 12.3)
Baseline OFC performed	3 (10.7)
Buildup (n = 28)	
Highest grade of reaction during baseline OFC/buildup	
No reaction	9 (32.1)
Grade 1	8 (28.6)
Grade 2	11 (39.3)
Grade 3	0
Grade 4	0
Epinephrine administered during buildup	1 (3.57)
Maintenance visits (n = 21)	
Highest grade of reaction during maintenance	
No reaction	20 (95.2)
Grade 1	1 (4.80)
Grade 2	0
Grade 3	0
Grade 4	0
Epinephrine administered during maintenance	0
Exit OFC (n = 21)	
Highest reaction grade during exit OFC	
No reaction	18 (85.7)
Grade 1	1 (4.80)
Grade 2	2 (9.50)
Grade 3	0
Grade 4	0
Epinephrine administered during exit OFC	0

Data are presented as nos. (%) unless otherwise indicated. Two patients with tree nut allergy did not receive tree nut OIT, but all others received tree nut OIT either before or after completion of sesame OIT. *IQR,* Interquartile range.
*All patients with peanut allergy had peanut OIT completed before sesame OIT.

Disclosure of potential conflict of interest: S. C. Erdle has been a member of an advisory board for ALK and has received an educational grant from Pfizer. M. McHenry and G. A. Rex have been members of advisory board for Sanofi Genzyme. S. Kapur has been member of advisory boards for Sanofi Genzyme, Bausch, Pfizer, and Kaleo. V. E. Cook has been a member of advisory boards for Sanofi Genzyme, Bausch Health, and ALK; and has received honoraria from Aralez Pharmaceuticals, ALK, Pfizer, and CSL Behring. S. B. Cameron has been a member of advisory boards for ALK, Bausch, Medexus, Miravo Health, Pfizer, and Sanofi; and was a committee member of the Canadian Society of Allergy and Clinical Immunology (CSACI) oral immunotherapy guidelines. E. S. Chan has received research support from DBV; has been a member of advisory boards for Pfizer, Pediapharm, Leo Pharma, Kaleo, DBV, AllerGenis, Sanofi Genzyme, Bausch Health, and Avir Pharma; is a member of the health care advisory board for Food Allergy Canada; and was colead of the CSACI oral immunotherapy guidelines. J. Yeung has been a member of advisory boards of Johnson & Johnson, Stallergenes Greer, LEO Pharma, Miravo, and Sanofi Genzyme; and has received speaking honoraria from Pediapharm, Medexus Pharma, and Bausch Health. The rest of the authors declare that they have no relevant conflicts of interest.

Clinical implications:

- **High doses of tahini can be unpalatable to children, affecting adherence to sesame OIT.**
- **Preliminary evidence indicates that 200 mg maintenance protein is safe and effective in preschoolers.**

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