

Efficacy and Safety of Sesame Oral Immunotherapy—A Real-World, Single-Center Study



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What is already known about this topic? Sesame avoidance, the only current treatment for sesame allergy, is becoming harder to perform with the increasing presence of sesame in Western diet. Oral immunotherapy is effective in desensitizing milk, peanut, and egg allergy.

What does this article add to our knowledge? Sesame oral immunotherapy is highly effective, desensitizing more than 88% of allergic patients, and is associated with immunologic markers of desensitization. Adverse reactions, with some requiring epinephrine, occur during build-up, but their rate declines significantly during maintenance.

How does this study impact current management guidelines? The promising results of this study could be used to drive further prospective randomized controlled studies that would eventually enable the inclusion of sesame in formal recommendations for oral immunotherapy.

BACKGROUND: The presence of sesame in Western diet is increasing, making its avoidance by sesame-allergic patients more challenging.

OBJECTIVE: To report the efficacy and safety of sesame oral immunotherapy (OIT).

METHODS: Sixty patients aged 4 years or older, diagnosed as sesame-allergic on the basis of a positive oral food challenge, were consecutively enrolled into OIT between November 2014 and November 2017. Fifteen patients with sesame allergy, based on a positive oral food challenge or a recent immediate reaction, and a positive skin prick test result or specific IgE, continued sesame elimination and served as observational controls. Immunologic parameters were measured in a subset

(OIT, $n = 16$; controls, $n = 11$) at the start and end of the study. Fully desensitized patients continued daily consumption of 1200 mg sesame protein and challenged with 4000 mg after more than 6 months.

RESULTS: Fifty-three OIT-treated patients (88.4%) were fully desensitized to sesame, compared with 0% of controls. Four additional patients (total 57 of 60 = 95%) were desensitized to more than 1000 mg protein. Reactions occurred in 4.7% of hospital doses and 1.9% of home doses. Epinephrine-treated reactions occurred in 16.7% of patients for hospital and 8.3% for home doses. Significant decreases in rSes i 1 IgE ($P = .007$) and basophil reactivity ($P = .001$) and increases in sesame and rSes i 1 IgG₄ ($P = .001$) occurred in OIT-treated patients but not in controls. Forty-seven patients desensitized to 4000 mg were evaluated more than 6 months after reaching maintenance. Only mild reactions were reported during maintenance, and all passed the 4000-mg challenge.

CONCLUSIONS: Sesame-OIT is an effective alternative to sesame avoidance in allergic patients. The potential for adverse events necessitates its performance in specialized centers. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2775-81)

Key words: Sesame allergy; Oral immunotherapy; OIT; Desensitization; OFC; Oral food challenge

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M.R.G. is funded by a Kamea grant from the Ministry of Health, Israel. Y.K. is supported by the Leon Alcalay Chair in Pediatric Immunology, Tel Aviv University, Israel.

Conflicts of interest: M. Holmqvist and J. Lidholm are employees of Thermo Fisher Scientific. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication February 27, 2019; revised April 30, 2019; accepted for publication May 21, 2019.

Available online May 29, 2019.

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2213-2198

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<https://doi.org/10.1016/j.jaip.2019.05.031>

INTRODUCTION

Sesame-allergic patients are at risk for severe and potentially life-threatening reactions in the event of accidental exposures to sesame and their quality of life is often impaired.¹ The reported prevalence of allergy to sesame is 0.2% to 0.8%.^{1,2} Unlike allergies to milk and egg, which are characterized by high rates of

Abbreviations used

BAT- basophil activation test

HPSE- high-protein sesame extract

OFC- oral food challenge

OIT- Oral immunotherapy

SP- sesame protein

SHTD- single highest tolerated dose

SPT- skin prick test

spontaneous recovery, only 20% to 30% of sesame-allergic patients acquire natural tolerance to sesame and most will have to lead a life of avoidance, long-term.^{1,3-5} The standard care of sesame-allergic patients consists of strict sesame avoidance and the use of injectable epinephrine in case of a severe reaction on unintended exposure to sesame.⁶ In recent years, given the increased awareness of sesame's nutritional benefits, it has become more prevalent in Western diet.⁷ As a result, the practice of sesame avoidance has become more challenging, the risk of accidental exposures resulting in anaphylactic reactions has increased, and quality of life of sesame-allergic patients is further impaired. The risk of fatal reactions to sesame is highlighted by 2 fatalities of sesame-allergic patients who were unaware of the sesame content of their food.^{8,9} The latter events prompted the Food and Drug Administration to advance a new effort for the consideration of allergic labeling for sesame.¹⁰

Oral immunotherapy (OIT) has been investigated over the past decade as an alternative treatment for food-allergic patients.^{11,12} OIT demonstrates variable rates of desensitization for different food allergies, ranging from 55% to 90%.⁸⁻¹³ Recently, OIT was included in the European Academy of Allergy and Clinical Immunology guidelines as an optional treatment for milk, egg, and peanut allergy.¹⁴ Information regarding the efficacy and safety of OIT for the treatment of other foods, including sesame, is lacking. An OIT program for the treatment of patients with sesame allergy was initiated at Yitzhak Shamir (formerly Asaf Harofeh) Medical Center in November 2014. Treatment efficacy and the rate of adverse events in all patients enrolled between November 2014 and November 2017 were analyzed, and compared with those in a group of sesame-allergic patients who continued the standard care of sesame elimination. Associated immunologic changes during the study period were also compared.¹⁵

METHODS

Patients

Sixty patients aged 4 years or older with IgE-mediated sesame allergy were enrolled into an open-label OIT treatment program at the Institute of Allergy, Immunology and Pediatric Pulmonology at the Yitzhak Shamir (formerly Assaf Harofeh) Medical Center, Zerifin, Israel, between November 2014 and November 2017. Fifteen sesame-allergic patients who continued sesame elimination during that period served as observational controls. These patients were all eligible for OIT but refrained from treatment during the study period for nonmedical reasons, such as a large travel distance to the clinic or previous obligations at the time of their invite to treatment. Patients with uncontrolled asthma, chronic inflammatory disease, or chronic lung disease other than asthma were excluded. OIT-treated patients were all challenged to sesame during the first 2 days of OIT, as detailed below. The diagnosis of sesame allergy in

control patients was based on a positive oral food challenge (OFC) ($n = 6$) or a clinical history of an immediate (within 2 hours of exposure) reaction (cutaneous, gastrointestinal, respiratory, and/or systemic symptoms) to sesame following accidental ingestion in the past year together with evidence of sesame sensitization based on a positive skin prick test (SPT) result and/or specific serum IgE (≥ 0.35 kU_A/L) ($n = 9$). Blood was obtained from a random subgroup of patients in both groups, as a research add-on study, and analyzed for basophil reactivity, and for levels of IgE and IgG₄ to sesame and rSes i 1, at the beginning and end of OIT or the observation period. Approval for the performance of basophil activation test (BAT), antibodies measurements, and the documentation and publication of all patient data was obtained from the Helsinki Institutional Review Board Committee. Informed parental or patient (for those aged >18 years) written consent was obtained from all participants.

Pre-OIT assessment

A comprehensive medical history was obtained from each patient/parent including the occurrence of previous reactions, treatments provided including the use of injectable epinephrine, emergency department visits, and hospital admissions. Patients/parents were asked about other atopic diseases including additional food allergies and asthma. SPTs to sesame with both commercial (1:10 w/v; ALK-Abello, Port Washington, NY) and a standardized high-protein sesame extract (HPSE)¹⁶ were performed on the volar surface of the forearm of all patients with single-peak lancets (Heinz Herenz, Hamburg, Germany) and the mean wheal diameter was measured after 20 minutes. The HPSE, previously shown to more accurately diagnose sesame allergy compared with the commercial extract, was prepared from a low-fat, high-protein (46%) sesame flour (Sukrin) which was dissolved in water to a concentration of 100 mg/mL of protein.¹⁶ Histamine 1 mg/mL (ALK-Abello) and saline were used as positive and negative controls. A positive SPT result was defined as a wheal diameter that was at least 3 mm more than that of the negative control.

Sesame-OIT protocol

The build-up part of the program was similar to that of our previously described milk-OIT, peanut-OIT, and walnut-OIT.¹⁷⁻¹⁹ The HPSE preparation, in its liquid form, was used for OIT doses of less than 240 mg of sesame protein (SP). Sesame doses of greater than or equal to 240 mg SP were given as raw Tahini (1 g Tahini = 240 mg SP). The initial 2 days of the first dose-escalation round served as an entry OFC up to 4800 mg SP (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Because a reaction to sesame was mandatory for inclusion in the OIT group, patients who did not react were classified as nonallergic and excluded. The following 2 days served to identify the single highest tolerated dose (SHTD), defined as the maximal amount of SP patients could safely consume. The SHTD was then consumed at least once daily at home for 24 days. Subsequently, patients returned for monthly dose escalations performed in an ambulatory day care setting, followed by monthly periods of home treatment with fixed doses of SP (see additional details in this article's Online Repository at www.jaci-inpractice.org). Patients who could tolerate the goal dose of 4000 mg SP, as previously used by others²⁰ at the end of build-up, were considered fully desensitized. Patients who could tolerate greater than or equal to 240 mg SP (equivalent to 1 g of Tahini) but less than 4000 mg SP were considered partially desensitized and instructed to regularly consume their highest tolerated

dose. Patients who were unable to tolerate 240 mg SP at the end of build-up were considered treatment failures. No dose increases were allowed at home. A staff physician was on call 24/7 for consultation and patients were instructed to send daily detailed reports of their home dose consumption via a Web-based reporting system or e-mail (see detailed information in this article's Online Repository and in Nachshon et al²¹). Adverse reactions during in-hospital treatment were categorized on the basis of World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System.²²

BAT and component-resolved diagnostics

BATs were performed in a randomly selected group of 16 patients from the OIT-treated patients and in 11 observational controls at study entry, and once again after the end of the study (desensitization in OIT-treated patients and end of the observation period in controls). Information regarding BAT performance is detailed in this article's Online Repository at www.jaci-inpractice.org (and in Vickery et al¹³). Serum was obtained from the 27 patients described above and measurements of specific IgE and IgG₄ antibodies to sesame and its component rSes i 1 were performed by ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden).

Maintenance phase

Patients who achieved 4000 mg SP were instructed to consume a daily maintenance dose of 1200 mg SP (5 g of Tahini). This low-maintenance dose was previously demonstrated to improve long-term adherence to peanut-OIT,¹⁸ as well as effective for preserving full desensitization.^{18,19} Ad lib consumption of additional sesame-containing products was allowed (with at least 2-hour interval from the maintenance dose). Patients who achieved at least 240 mg but did not achieve 4000 mg SP were instructed to consume their achieved dose for an unlimited time. All patients were advised to continue carrying injectable epinephrine at all times and were informed about the risk of sesame allergy recurrence in the case of discontinuation of regular consumption of SP. Electronic reporting during the maintenance phase was mandatory only for cases of reactions. All patients who had reached both full or partial desensitization by April 2018 and continued its regular maintenance dose consumption for 6 or more months were invited for a follow-up visit. Information about sesame maintenance consumption, reactions experienced, and treatments given was obtained. Given that Ad lib sesame consumption was infrequent and irregular, this information was not analyzed. SPT with both commercial sesame extract and HPSE was performed. All patients underwent an OFC to 4000 mg of SP.

Statistical analysis

We calculated that 50 sesame-allergic participants (40 receiving OIT and 10 controls) would provide 90% power at a 2-sided 5% alpha, based on the assumption of 60% desensitization success rate in the OIT group and 10% in controls. Differences between the 2 groups were analyzed using Fisher exact test for categorical variables and the Mann-Whitney tests for continuous variables. Changes in SPT, BAT, and antibody levels in OIT-treated patients and controls, between the beginning and the end of the study, were examined using Wilcoxon signed ranks test. All analyses were 2-tailed, and a *P* value of less than .05 was considered significant. Statistical analyses were performed using SPSS software (version 20; SPSS, Inc, Chicago, Ill).

RESULTS

Outcome of OIT versus control

Fifty-three of the 60 OIT-treated patients (88.3%) were desensitized to 4000 mg SP (Figure 1). Median duration of treatment until achieving maintenance dose was 6.5 (interquartile range, 3.8-12.8) months. Seven additional OIT-treated patients were partially desensitized to greater than or equal to 240 mg SP. The observational control group was reevaluated 7 to 37 (median, 26.8) months after their enrollment. None of the control patients was tolerant to sesame at the end of the study. Two patients experienced anaphylactic reactions to sesame during this period, occurring more than 6 months after their initial enrollment. Another 9 patients were challenged, and all had a positive OFC. The remaining 4 patients were not exposed to sesame during the observation period. However, their SPT wheal diameter was at levels greater than 95% positive predictive value for sesame allergy both at the start and at the end of the study,¹⁶ and was either unchanged or larger at the end of the study compared with that at first evaluation. The OIT and control groups were comparable in demographic characteristics, the presence of asthma and other food allergies, and the severity of reactions to sesame before study enrollment (Table I).

Adverse reactions occurred in 127 of 2,720 (4.7%) induction doses and 253 of 13,170 (2%) home doses during the course of OIT. All patients experienced at least 1 reaction, during at least the first induction round, per our protocol (see Table E1), except for 2 patients who had a diagnostic OFC few weeks before entering OIT. During the hospital build-up phase, epinephrine was administered to 10 patients (16.7%) for 13 of 127 (9.4%) reactions. During home treatment epinephrine was used by 5 patients (8.3%) for 7 of 253 (2.8%) reactions. The type and severity of reactions occurring during build-up are presented in Table E2 in this article's Online Repository at www.jaci-inpractice.org. Only reactions graded as I or II according to the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System were experienced during the study.²² Nonanaphylactic gastrointestinal symptoms (gastrointestinal symptoms, including occasional abdominal pain, nausea, and vomiting, not within the 2 hours after dose administration) occurred in 3 patients and were accompanied by a temporal increase in peripheral blood eosinophils. The symptoms and eosinophilia in these 3 patients resolved after a month in which temporally lower doses were administered, as previously described.²³ Eventually, these 3 patients were fully desensitized to 4000 mg of SP.

We next explored risk factors for failure to achieve full sesame desensitization (Table II). Seven OIT-treated patients (11.7%) were partially desensitized to 240 to 3600 mg SP (Figure 1). All pretreatment characteristics, including age, sex, physician-diagnosed asthma, and having other food allergies, were comparable between patients who achieved full or partial desensitization. Also, there were no significant differences between the 2 groups in the rate of reactions to home doses, the rate of epinephrine treatments for hospital and home reactions, and the presence of non-anaphylactic gastrointestinal symptoms. Severe pre-OIT reactions to sesame were more frequent in patients who failed to reach full desensitization but this was not statistically significant. The only predictors for failure to achieve full desensitization were a low SHTD at the beginning of treatment and a high rate of reactions to doses administered during build-up hospital visits (Table II).

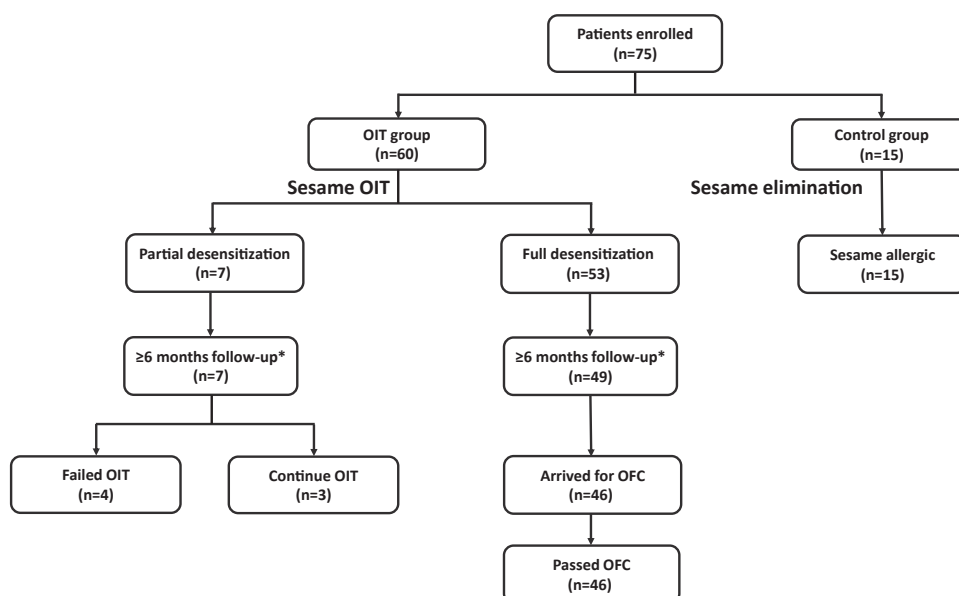


FIGURE 1. Study enrollment and clinical outcomes in the OIT and observational control groups. A flow diagram is presented demonstrating patients' enrollment into the OIT group or the observational control group and their clinical outcomes after treatment or observation, respectively. Patients fully desensitized to sesame were challenged with a high dose of sesame (4000 mg) after 6 months of low-dose (1200 mg) consumption. Sesame partial desensitization was defined by a highest tolerated dose greater than or equal to 240 mg but less than 4000 mg SP. *Only patients with greater than or equal to 6-month maintenance dose consumption were invited for follow-up and OFC.

TABLE I. Baseline demographic and clinical characteristics of the study population

Parameter*	OIT (n = 60)	Control (n = 15)	P value
Age (y)	7.5 (5.8-11.6)	7 (5.6-11.3)	.9
Male sex	37 (61.7)	11 (73.3)	.55
Other food allergies	42 (70)	14 (93.3)	.1
Asthma	36 (60)	8 (53.3)	.77
Previous anaphylaxis	21 (35)	3 (20)	.36
Previous epinephrine use	16 (26.7)	2 (13.3)	.5
Previous ER visit	22 (36.7)	4 (26.7)	.56
Previous hospitalization	4 (6.7)	2 (13.3)	.59
Sesame SPT-commercial (mm)	6 (4-7)	4 (0-7)	.04
Sesame SPT-HPSE (mm)	11 (8-15)	11 (9-14)	.85

ER, Emergency room.

*Categorical variables are presented as mean (%). Continuous variables are presented as median (interquartile range).

Almost all (97.6%) patients with SHTD greater than 22.5 mg SP achieved full desensitization compared with 66.7% of the patients with an SHTD value of less than or equal to 22.5 mg ($P = .002$) (Figure 2).

Immunologic correlates

Immunologic measures in OIT-treated and control patients at the beginning and the end of the study were compared. SPT wheal size to commercial sesame extract (Figure 3, A) and HPSE (Figure 3, B) decreased significantly in the OIT group ($P < .001$) but not in controls (HPSE, $P = .36$; commercial SPT, $P = .26$). Sesame-induced CD63 ($P = .001$) (Figure 3, C) and CD203c ($P = .015$) (Figure 3, D) expression also significantly decreased

after OIT but not after the observation period of the control group ($P = .33$ and $P = .23$, respectively). Following sesame-OIT treatment, IgE levels (Figure 4, A) did not significantly change ($P = .12$), but the level of IgG₄ to sesame (Figure 4, B) significantly increased ($P = .001$), leading to a significant decrease in the IgE/IgG₄ ratio ($P = .001$) (Figure 4, C). In contrast, no significant changes in the levels of IgE ($P = .72$), IgG₄ ($P = .11$), or IgE/IgG₄ ratio ($P = .59$) to sesame were observed in control patients. Similarly, there was a significant decrease in the levels of IgE ($P = .007$) (Figure 4, D), increase in IgG₄ ($P = .001$) (Figure 4, E), and decrease in IgE/IgG₄ ratio ($P < .001$) (Figure 4, F) to rSes i 1 in OIT-treated patients, in contrast to controls, in which no significant change in IgE ($P = .66$), IgG₄ ($P = .29$), or IgE/IgG₄ ratio ($P = .72$) to rSes i 1 was noted (Figure 4).

Maintenance phase follow-up

Of the 53 fully desensitized patients, 49 were already at more than 6 months after reaching maintenance at the time of the evaluation for follow-up; 46 of them (89.4%) arrived for a follow-up visit after a median maintenance phase of 8 months (range, 5.5-34.6). The remaining 3 patients continued regular sesame consumption but were unavailable for OFC. All patients reported regular maintenance dose consumption of at least 1200 mg SP, and only 2 patients experienced a few mild reactions. No reactions requiring epinephrine were reported during this period. All 46 patients passed the 4000 mg SP challenge (Figure 1). The 7 partially desensitized patients were instructed to continue regular consumption of their maximal reached dose. Four of these patients discontinued treatment after several months (2 patients because of difficulty in incorporating the regular dose with their daily activities, and another 2 because of food

TABLE II. Comparison of patients based on status at end of build-up

Treatment stage	Parameter	Group 1 desensitized to >4000 mg (n = 53)	Group 2 desensitized to 240-3600 mg (n = 7)	P value
Demographic characteristics	Male sex	34 (64.1)	3 (42.9)	0.41
	Age (y)	7.4 (3.8-27.1)	9.2 (5.5-27)	0.276
	Other food allergies	38 (71.7)	4 (57.1)	0.42
Pre-OIT	Asthma	33 (62.2)	3 (42.9)	0.42
	Anaphylaxis	20 (37.7)	1 (14.9)	0.4
	Injectable epinephrine	13 (24.5)	3 (42.9)	0.37
	Emergency room	18 (34)	4 (57.1)	0.41
	Hospitalization	3 (5.7)	1 (14.3)	0.4
	SPT wheal size-commercial (mm)	6 (0-11)	5 (0-12)	0.35
	SPT wheal size-HPSE (mm)	11 (4-28)	12 (8-25)	0.34
Build-up	SHTD (mg)	90 (2-1440)	20 (12-90)	0.013
	Reactions-hospital (#)	4 (0-13)	7 (4-10)	0.006
	Epinephrine-hospital	8 (15)	2 (28.6)	0.33
	Reactions-home (#)	1 (0-7.5)	2 (0-6)	0.79
	Epinephrine-home	4 (7.5)	1 (14.2)	0.48
	NAN GI symptoms	3 (5.7)	0 (0)	1.0

ED, Eliciting dose; GI, gastrointestinal; NAN, nonanaphylactic.

Categorical variables are presented as mean (%). Continuous variables are presented as median (range).

Bold indicates statistical significance ($P < .05$).

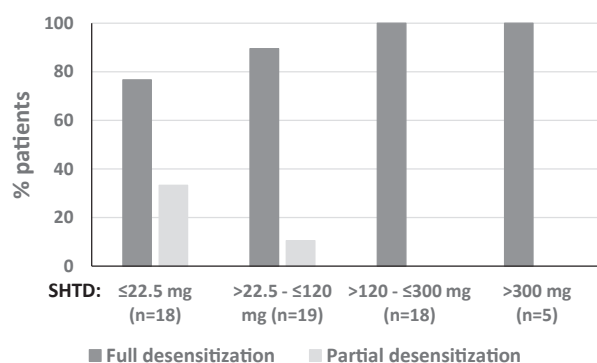


FIGURE 2. Treatment outcome according to the highest tolerated starting dose. Treatment outcome at the end of build-up for patients reaching full (4000 mg) or partial (240 to <4000 mg) desensitization is shown for groups categorized according to the SHTD at initial escalation week.

aversion). The remaining 3 patients continued regular maintenance dose consumption (480, 1200, and 3600 mg SP) with no allergic reactions reported.

DISCUSSION

This is the first study to describe the course and outcome of OIT for sesame allergy. It demonstrates that sesame-OIT is highly effective, providing full desensitization in 88% and an increase in tolerated dose to greater than or equal to 1200 mg in 95% of patients. As previously shown for other foods, the treatment is associated with adverse events in most patients, some requiring epinephrine. Daily consumption of a relatively low daily dose is well tolerated and sufficient to maintain full desensitization.

The overall success rate of sesame-OIT in this study is higher than that of our previously described milk-OIT and is comparable with those previously reported in peanut-OIT trials as well

as with our own experience with peanut- and walnut-OIT.^{11,17-19} Similar to observations made for other foods, desensitization to sesame was associated with immunologic changes (a decrease in SPT wheal diameter, serum levels of sesame IgE and basophil reactivity to sesame, and an increase in IgG₄ to sesame and the major sesame allergen Ses i 1), suggesting a potential future development of immune tolerance.^{20,24,25}

Several parameters were associated with a lower rate of achieving full desensitization. These include a low SHTD and reactions experienced during build-up. These factors likely reflect a more severe form of sesame allergy and are in line with previous OIT studies for milk, peanut, and tree-nut.¹⁷⁻¹⁹ We have previously found that milk-allergic patients with persistent asthma are less likely to achieve full desensitization during milk-OIT.^{17,26} In contrast, in this study, as in peanut- and walnut-OIT,^{18,19} asthma comorbidity did not affect sesame-OIT outcome. Similarly, patients with additional food allergies were as likely to achieve full desensitization as patients with an isolated sesame allergy. An inability to achieve full desensitization was found to be a risk factor for discontinuing OIT later on.

The efficacy of OIT as a treatment for patients with allergies to milk, egg, and peanut has been demonstrated in multiple studies.^{11,12} This has led to the development of guidelines by the European Academy of Allergy and Clinical Immunology, stating that OIT should be offered to patients with milk, egg, or peanut allergy.¹⁴ However, because of the lack of evidence, OIT could not be recommended as a treatment option for other food allergies. Yet, the need for an OIT treatment program to sesame is growing given the increasing frequency of sesame in Western diet and the risks to patients on inadvertent exposure.^{1,7-9} In the current study, we show for the first time, using a controlled study design, that sesame-OIT is effective and safe when administered in a supervised environment. Sesame allergy did not resolve in any patient of the control group during the study, consistent with previous information of low childhood resolution rate of sesame allergy.¹

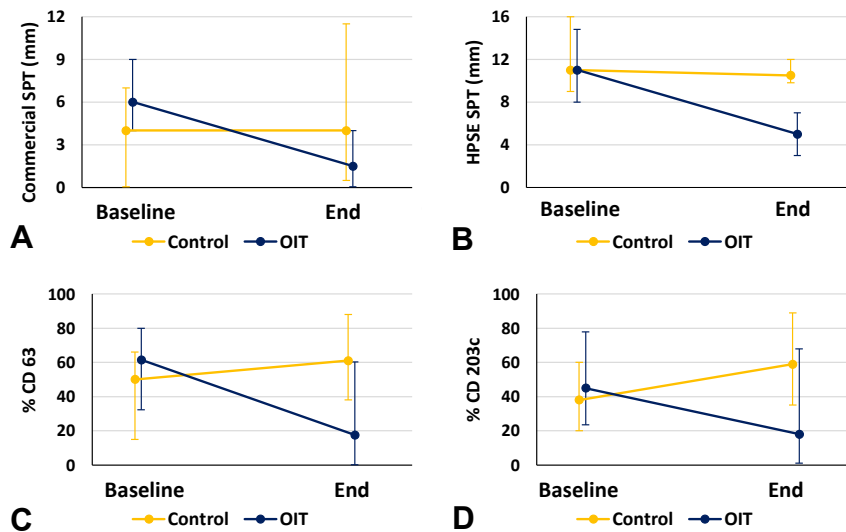


FIGURE 3. Changes in cellular immune response in OIT versus control patients. Medians (interquartile range) of sesame commercial SPT (A), HPSE SPT (B), basophil activation: CD63 (C) and CD203c (D) expression in OIT-treated patients versus controls from study start to end date. Data are available for commercial SPT (n = 28), HPSE SPT (n = 45), basophil activation: CD63 and CD203c (n = 16) patients in the OIT group and for commercial SPT (n = 11), HPSE SPT (n = 14), basophil activation: CD63 and CD203c (n = 11) patients in the control group. Significant changes were noted for all variables in the OIT group only.

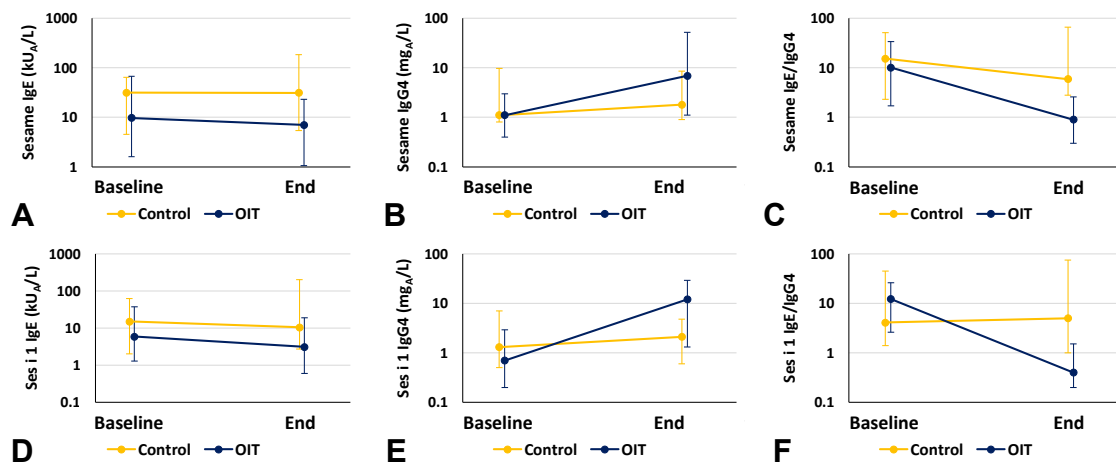


FIGURE 4. Changes in humoral immune response in OIT versus control patients. Medians (interquartile range) of sesame IgE (A), IgG₄ (B), and IgE/IgG₄ ratio (C) and of Ses i1 IgE (D), IgG₄ (E), and IgE/IgG₄ ratio (F) in OIT-treated patients versus controls from study start to end date. Data are available for 16 patients in the OIT group and for 11 patients in the control group. Except for sesame IgE, significant changes were noted for all variables in the OIT group. There was no significant change in the control group from start to end of study.

Various studies demonstrated that most OIT patients lose their state of desensitization after different withdrawal periods.^{20,25,27-30} These results illustrate that OIT in most patients maintains a state of desensitization dependent on a regular consumption of the allergenic food. Unfortunately, the need for patients' long-term cooperation with regular dose consumption results in difficulty to implement a successful OIT treatment program.³⁰ We previously found that decreasing peanut-OIT maintenance dose from 3000 mg to 1200 mg peanut protein improves long-term adherence of patients to treatment.¹⁸

Moreover, daily consumption of a dose of 1200 mg protein preserved full desensitization in patients who underwent OIT for peanut (3000 mg)¹⁸ or walnut (4000 mg).¹⁹ Similarly, in this study, we demonstrate that all sesame-allergic patients who were tested more than 6 months after achieving full desensitization were able to continue regular consumption of 1200 mg protein and still maintained desensitization to 4000 mg (Figure 1). Although some patients consumed additional sesame-containing products, this happened infrequently and irregularly, and was therefore not analyzed. Most patients consumed the daily dose

only, because of sesame food aversion. It is likely that such a relatively low maintenance dose will facilitate patients' long-term compliance and preserve the OIT-induced desensitization. Whether even lower doses are sufficient to maintain the fully desensitized state requires further study.

This study has several limitations. First, this study was not randomized or blinded. However, all patients in the control group were eligible for OIT and were either waiting to begin treatment or unable to undertake it during the study period because of previous obligations or practical reasons. Furthermore, the 2 study groups were matched in baseline characteristics and markers of severity of sesame allergy. In addition, the objective assessment of patients using OFCs at the start of treatment and at the end of the study, together with the associated immunologic changes, provide further support to our findings. To further minimize the risk of bias, all OFCs were performed by trained allergists and only objective symptoms served as criteria for determining a positive OFC. In addition, accurate grading of home treatments was not done. However, the continuous electronic documentation, together with the phone call availability, provides us with good information regarding patients' home treatments and reactions and minimizes recall bias. Finally, this is a single-center study and its results should be examined in other centers, on different populations.

In summary, this study presents promising short- and long-term results for desensitization of sesame-allergic patients. Similar to previous OIT trials, severe anaphylactic reactions requiring injectable epinephrine may occur and therefore the treatment should be performed only under appropriate conditions in food allergy specialized centers. However, the minimal rate of adverse reactions during maintenance is encouraging. The continuous threat of anaphylactic reactions and impaired quality of life in sesame-allergic patients, together with the promising results of this study, should be used to drive further prospective randomized controlled studies that would enable the inclusion of sesame in formal recommendations for OIT.

Acknowledgments

We thank Hasia Duani and Tehila Abargil for coordinating the patient clinical visits.

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ONLINE REPOSITORY

BASOPHIL ACTIVATION TEST

To generate a solubilized extract for basophil stimulation, whole sesame seeds were ground and pestled in water, followed by a centrifugation of the mixture at 14,000 RCF for 15 minutes at 4°C. The protein concentration of the supernatant was measured (DC Protein Assay, Bio-Rad, Berkely, Calif) and 1 mg/mL stocks were stored at -20°C. Whole blood was drawn from patients using a winged infusion set and syringe and placed into Vacutainer tubes. The blood was then diluted 1:1 in RPMI 1640 (Biological Industries, Beit HaEmek, Israel), containing 1 ng/mL of recombinant human IL-3 (R&D Systems, Minneapolis, Minn), sesame seed protein supernatant (1 µg/mL), and the following fluorochrome-conjugated antibodies: allophycocyanin antihuman CD63 (clone H5C6) purchased from BioLegend (San Diego, Calif), fluorescein isothiocyanate-antihuman CD123 (clone 6H6), R-phycoerythrin-Cy7 antihuman HLA-DR (clone LN3), and R-phycoerythrin antihuman CD203c (clone NP4D6), purchased from ThermoFisher (Waltham, Mass). Baseline stimulation tubes were set up in the presence of IL-3 and staining antibodies but without the addition of SP. All tubes were incubated for 15 to 20 minutes in a 37°C waterbath. 2 mM EDTA was then added to each tube to stop basophil reaction. Erythrocytes were lysed (ThermoFisher) at room temperature in the presence of 2 mM EDTA. Cells were centrifuged (500g, 4°C, 8 minutes), and resuspended in FACS reading buffer (PBS + 2 mM EDTA). Cells were acquired on a flow cytometer (Beckman FC-500, or Navios) with basophils identified as CD123⁺ HLA-DR⁻ cells. The induced expression of CD63 and CD203c was quantitated in approximately 300 identified basophil cells per sample. Analysis was performed using Flowing Software 2.5.1 (Turku Centre for Biotechnology, University of Turku, Finland), by an individual blinded to patient OIT status. The percentages of basophils expressing CD63 or CD203c in the presence of sesame above the levels of patient basophil expression of these markers in IL-3 alone were evaluated for each patient at each time point.

SESAME-OIT PROTOCOL

The initial days of the first dose-escalation round served as an OFC up to 4800 mg SP (Table E1). Patients who did not react were classified as nonallergic and excluded. A reaction was diagnosed only in the case of objective signs of allergic reaction (urticarial rash, rhinitis/sneezing or conjunctival congestion, cough/wheezing, vomiting, or a decline in blood pressure, and a persistent abdominal pain). If a reaction occurred, the following days served to identify the SHTD, defined as the maximal amount of SP the patients could safely consume. Following the initial dose-escalation week, patients were instructed to consume the SHTD daily at home for 24 days under parental supervision for 1.5 hours. Patients were instructed to avoid physical activity 30 minutes before and 2 hours after the dose, and not to take the dose on an empty stomach. Anticipatory home treatment guidance to patients and parents was given. Each patient received antihistamines, bronchodilators, and 2 up-to-date Epi-Pens with instructions to administer at any severe reaction (severe abdominal pain, dyspnea, or apathy). A staff physician was on call 24/7 for consultation for urgent cases. In addition, patients were instructed to send a daily report of their home dose consumption, including a questionnaire about any experienced reactions and any treatments provided, via a Web-based reporting system, or, in special occasions, via an e-mail.^{E1} Patients' electronic reports were followed continuously by staff members and patients were connected and instructed (via e-mail ± phone call) regarding any required changes in their treatment. A 30% reduction in the daily dose and antihistamine for 5 days was recommended if mild reactions occurred and/or during viral infections. Dose reduction by 30% for the duration until the next up dosing in clinic was performed in cases of repeated or severe reactions requiring adrenaline. The first home treatment period was followed by a second 4-day up dosing cycle with a goal of 4-fold dose increase. This was followed again by 24 days of fixed dose (new SHTD) consumption at home. The third cycle consisted of 3 days with a goal of 3-fold dose increase. The fourth and fifth cycles consisted of 2 days each with a 2-fold dose increase. Following that, patients arrived for 1-day cycles with a goal of 50% dose increase until the goal of greater than 4000 mg SP was achieved.

TABLE E1. First week sesame-OIT protocol

Day	Dose	Amount (mg SP)	Tahini (g)	Interval (min)
Day 1	1	0.3		0
	2	3		15
	3	15		15
	4	30		15
	5	60		30
	6	120		60
	7	120*		90
	—	Observation		90
Day 2	1	120		0
	2	180		30
	3	240	1	30
	4	480	2	30
	5	960	4	30
	6	2880	12	45
	7	4800	20	60
	—	Observation		90
Day 3	1	Last tolerated dose		0
	2	A dose between RD and last tolerated dose		90
	3	A dose between RD and last tolerated dose		90
	—	Observation		90
Day 4	1	SHTD		0
	2	SHTD		90
	—	Observation		90

RD, Reaction dose.

*If no reaction occurred on day 1, the protocol continued to day 2. Once a reaction occurred, the following days were used to determine the maximal dose that could be safely consumed by the patient.

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TABLE E2. Induction and home adverse reactions during the OIT build-up phase

Phase	Adverse reactions	Per patient %	Per dose %
Inductions	Any	95	4.7
	Perioral	7	0.3
	Skin	26.8	1.25
	Upper respiratory	42.5	2
	Eye	10.2	0.5
	Lower respiratory	9.4	0.4
	Gastrointestinal	53.5	2.5
	Cardiovascular	0	0
	Nonresponding asthma	0	0
	Upper airway block	0	0
	≥2 systems	32.3	1.5
	Grade 1	51.2	2.4
	Grade 2	48.8	2.3
	Epinephrine	16.7	0.5
	Antihistamines	64.6	3
Home	Bronchodilators	9.4	0.4
	No reaction	35	0.16
	A single reaction	15	Na
	2-4 reactions	23	Na
	≥5 reactions	27	Na
	Epinephrine	8.3	0.05
	Overall reactions	65	1.92

Induction adverse reactions are based on the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System.^{E2}

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