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Long-term outcome of peanut oral immunotherapy—Real-life experience

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Abstract

Background: Oral immunotherapy (OIT) is currently recommended as a treatment option for peanut-allergic patients. Data regarding its long-term compliance and efficacy in real life are required.

Methods: Peanut-allergic patients aged ≥ 4 years were enrolled in a single-center clinical OIT program. Buildup to 3000 mg peanut protein was performed. Patients reaching this dose before or after 12/2014 were instructed to consume 3000 or 1200 mg daily, respectively. Patients were followed ≥ 6 months after reaching maintenance and rechallenged to 3000 mg.

Results: Of the 145 patients studied, 113 (77.9%) were fully desensitized to 3000 mg and 133 (91.7%) were desensitized to ≥ 300 mg. 21/145 patients (14.5%) required adrenaline for home-dose reactions during buildup. Non-anaphylactic gastrointestinal symptoms, experienced by 9 patients (6.2%), reversed with dose reduction. Of the 111 patients available for analysis 6 months after reaching 3000 mg, 97 (87.4%) continued regular peanut consumption. Only 2/111 patients (1.8%) required adrenaline over the long-term (median, range; 18, 6-75 months) follow-up. Adherence to treatment was significantly higher in patients consuming 1200 mg (73/76, 96.1%) vs those consuming 3000 mg (24/35, 72.2%), ($P = .001$). A higher maintenance dosage and home adrenaline requirement during buildup predicted adherence cessation (OR 12.5, $P = .001$; and OR 7.8, $P = .02$, respectively). 63/64 patients (98.4%) consuming 1200 mg maintenance dose were successfully rechallenged to 3000 mg.

Conclusions: This real-life experience demonstrates the efficacy of peanut OIT long-term. A lower maintenance dose minimized treatment cessation while maintaining desensitization. OIT should be performed in qualified centers given the prevalence of adverse reactions, particularly during buildup.

KEYWORDS

adverse reactions, desensitization, food aversion, maintenance dose, peanuts allergy

1 | INTRODUCTION

The standard care of patients with IgE-mediated food allergy consists of strict avoidance and the use of injectable adrenaline in case of reactions.¹ This approach is vulnerable to accidental exposures

which may result in severe anaphylactic and even fatal reactions²⁻⁵ and impairs patients' quality of life.⁴

In recent years, oral immunotherapy (OIT) has become a promising treatment alternative for patients with IgE-mediated food allergy.⁶⁻⁸ The success rate reported for OIT in desensitizing patients

with food allergy is high, ranging from 60% to 90%, depending on the food treated.^{6,7,18,19} Most allergic reactions during treatment are mild, although some require injectable adrenaline.⁹⁻¹³ Successful desensitization is associated with an immunological shift toward tolerance, including a reduction in SPT wheal diameter, increased levels of sIgG4, and decreased sIgE and basophil reactivity.^{14,15,19,20}

Various studies demonstrated that, while some patients achieve sustained unresponsiveness, after 1-3 months of treatment withdrawal, many subsequently lose it after longer withdrawal periods.^{13-16,19} These results illustrate that OIT in most patients maintains a state of desensitization dependent on the regular consumption of the allergenic food. For a clinical treatment program, a more realistic approach to prevent allergy recurrence would therefore be to recommend regular consumption of the allergenic food. However, the optimal dose required for that is unknown.^{6,7} Most previous studies aiming to fully desensitize peanut-allergic patients required regular consumption of high doses (3000-4000 mg) of peanut protein.^{14,15,17,18} While regular consumption of such high doses is feasible in randomized controlled studies, maintaining it in real life, where patient compliance and follow-up are different may prove difficult.^{6,7}

We describe real-life experience of a large number of patients treated at a single clinical center with a well-defined protocol and long-term follow-up period. We compared long-term compliance and desensitization status in patients consuming high (3000 mg) vs low (1200 mg) maintenance dose of peanut protein.

2 | METHODS

2.1 | Patients

Patients aged ≥ 4 years with IgE-mediated peanut allergy were enrolled into an open-label OIT treatment program at the Institute of Allergy, Immunology and Pediatric Pulmonology at the Assaf Harofeh Medical Center, Zerifin, Israel, between May 2010 and April 2016. Inclusion and exclusion criteria were previously described⁹ and are described in detail in the methods section of the Data S1. Informed parental or patient (>age 18) written consent was obtained from all participants. Data on the course and outcome of OIT were collected retrospectively. Helsinki committee approval for the documentation and publication of patient data was obtained.

2.2 | Peanut OIT protocol

The buildup part of the program was similar to that of our previously described milk-OIT program.⁹ The initial days of the first dose-escalation round served as an OFC up to 3000 mg peanut protein (Table S1). Patients who did not react were classified as non-allergic and excluded. If a reaction occurred, the following days served to identify the single highest tolerated dose (SHTD), defined as the maximal amount of peanut protein the patients could safely consume. The SHTD was then consumed at least once daily at home for 24 days. Subsequently, monthly rounds of ambulatory day care visit

for dose escalations were performed in clinic, followed by periods of 24 days of home treatment with fixed doses of peanut protein, until the goal of 3000 mg peanut protein was achieved (additional details in the Data S1). Patients who reached at least 300 mg peanut protein (equivalent to a single peanut) but had difficulty reaching 3000 mg were instructed to consume the dose they reached daily. Patients who could not reach 300 mg peanut protein were considered failures. No dose increases were allowed at home. A staff physician was on call 24/7 for consultation, and patients were instructed to send a daily detailed report of their home-dose consumption via e-mail or a web-based reporting system.²¹ Adverse reactions during in-clinic treatment were categorized based on the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System²²

2.3 | Maintenance phase

Patients were instructed to continue daily consumption of their final dose for unlimited time. All patients were advised to continue carrying injectable adrenaline at all times and were informed about the risk of peanut allergy recurrence in the case that regular peanut protein was discontinued. Electronic reporting during the maintenance phase was mandatory only for cases of reactions. Ad lib consumption of additional peanut-containing products was allowed for patients who reached the full dose of 3000 mg peanut protein. Given patients' report of difficulties in consuming such a high daily dose, we changed our instructions for patients who achieved 3000 mg after 12/2014, to consume a daily dose of only 1200 mg peanut protein.

2.4 | Follow-up

All patients who had reached both full or partial dose maintenance by December 2017 and continued treatment for ≥ 6 months were contacted. Information about peanut consumption, reactions experienced, and treatments given was obtained. Patients were asked whether their QOL perception following treatment was worsened, unchanged, or improved. Patients were invited to clinic where SPT and peanut OFCs were performed. All patients who reached 3000 mg and reported a regular dose consumption of at least three times per week were challenged with a single dose of 3000 mg peanut protein. Patients who reported irregular or rare (less than three times a week) peanut consumption and patients whose final dose was lower than 3000 mg underwent a graded OFC.

2.5 | Statistics

Statistical analyses were performed using SPSS software (version 20; SPSS, Inc, Chicago, IL, USA). The Mann-Whitney and Kruskal-Wallis tests were used for non-normally distributed continuous variables. Fisher's exact test was used to analyze differences in categorical variables. Multivariate analyses using logistic regression were used to determine significance of factors affecting the discontinuation of OIT. Kaplan-Meier curves and Cox regression analysis were used to

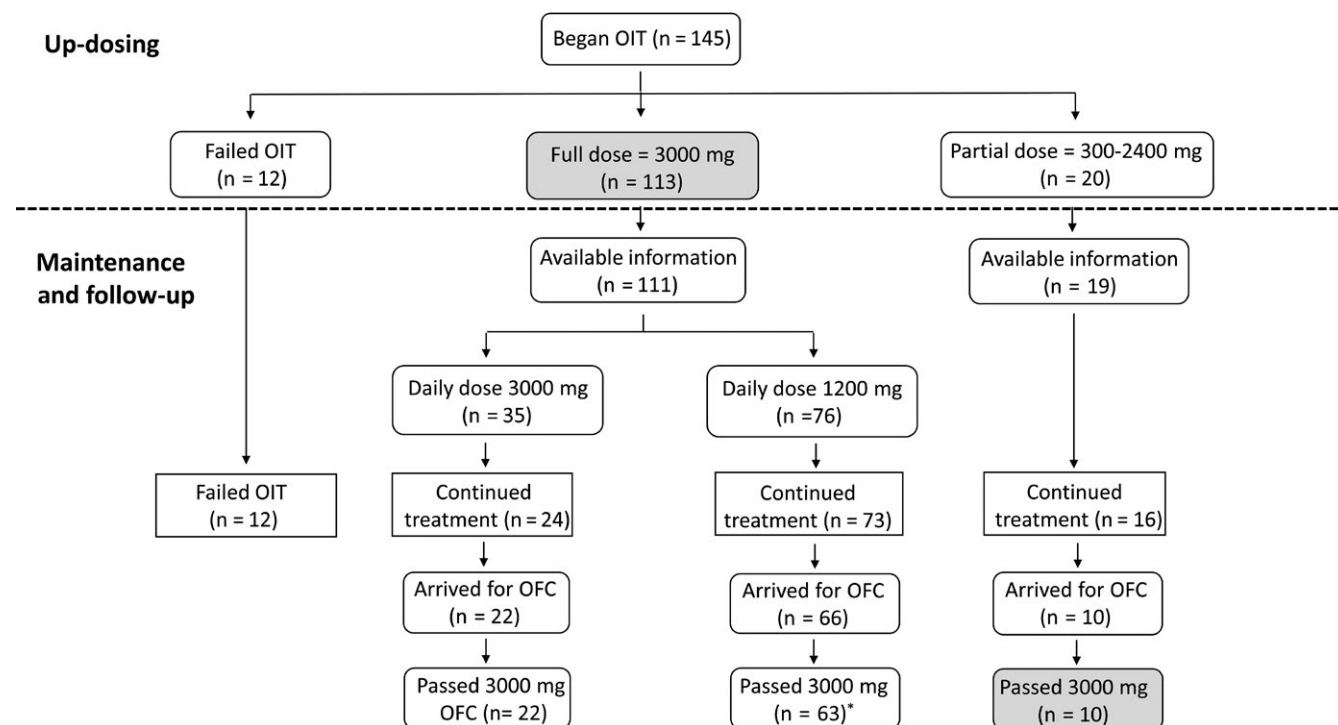


FIGURE 1 Oral immunotherapy treatment protocol and long-term follow-up of maintenance dosing. A flow diagram is presented demonstrating patient enrollment and OIT treatment outcomes after completion of the buildup phase (above dotted line) and long-term efficacy of high- vs low-dose full maintenance and partial dose maintenance (below dotted line) as determined by a full-dose (3000 mg) oral food challenge. *Two of the 3 patients who reacted after low-dose consumption were consuming <1200 mg protein against our recommendation

determine factors affecting time to discontinuing OIT. All analyses were 2-tailed, and a *P*-value of less than .05 was considered significant. Bonferroni correction was applied when multiple comparisons were made.

3 | RESULTS

3.1 | Buildup phase

Patient characteristics (demographic, pre-OIT, and during OIT) are shown in Table S2. Most patients were <11 years (*n* = 128, 88.3%), 11 (7.6%) were between 11-18 years, and 6 (4.1%) were >18 years old. The single highest tolerated dose (SHTD) during the initial dose-escalation week was <5 mg in 18 patients (12.4%) and <15 mg in 60 patients (41.3%). Description and severity of reactions occurring in clinic during buildup are shown in Table S3. Adrenaline was required for hospital and home doses in 18 (12.4%) and 21 (14.5%) patients, respectively. Non-anaphylactic gastrointestinal symptoms (GI symptoms not temporally related to dose administration) occurred in 9 patients and resolved with dose reduction.²³ Subsequently, 5 of these patients reached 3000 mg, one reached 1350 mg, and 3 patients discontinued treatment.

Of the 145 patients treated, 113 (77.9%) were fully desensitized to 3000 mg of peanut protein, 20 (13.8%) patients were partially desensitized to 300-2400 mg, and 12 patients (8.3%) failed (Figure 1). Patients who failed treatment were significantly younger compared

to those who were partially or fully desensitized (Table 1). Reasons for failing treatment were refusal to take the daily dose (*n* = 5), repeated reactions (*n* = 4; 1 in association with periodic fever, aphthous stomatitis, pharyngitis, and adenitis), and gastrointestinal symptoms unrelated to the dose (*n* = 3). Patients who reached full desensitization had significantly less reactions and reactions requiring adrenaline at home compared to the other 2 groups (Table 1).

We next evaluated the OIT course and outcome in asthmatics shown to be at increased risk of failing oral immunotherapy treatment.²⁴ 17/56 patients with asthma (30%) were using daily controller therapy before OIT. In an additional 30%, controller treatment was initiated during our pre-OIT evaluation. Forty-three asthmatics were able to perform spirometry with a mean baseline FEV1 = 101 ± 16%, FVC = 103 ± 20%, and FEV1/FVC = 94 ± 16%, and 9 patients (16%) had significant bronchodilator responsiveness. Although 23.2% of asthmatics vs 5.6% of non-asthmatics had SHTD <5 mg (*P* = .003), the 2 groups were comparable in pre-OIT reaction severity and in the course and outcome of OIT.

Another group requiring special attention are patients who require adrenaline during home buildup therapy (*n* = 21). These patients were markedly different as compared to those not requiring adrenaline treatments at home by their pre-OIT reaction severity. They had a significantly higher number of: anaphylactic reactions (66.7% vs 40.3%, *P* = .032), hospitalizations (23.8% vs 6.5%, *P* = .023), and reactions requiring adrenaline (42.9% vs 13.7%, *P* = .003). These patients also experienced a more difficult OIT course: more

TABLE 1 Comparison of patients based on status at end of buildup

Period	Parameter	Group 1 Desensitized to 3000 mg (n = 113)	Group 2 Desensitized to 300-2400 mg (n = 20)	Group 3 Failed (n = 12)
Demographics	Male gender	70 (62%)	13 (65%)	7 (58%)
	Age (y)	6 (4.5-8)	5.8 (4.6-7)	4.2 (3.9-5.9) ^a
	HDM sensitivity	82 (73.2%)	12 (63.2%)	9 (75%)
	Asthma	44 (39%)	9 (45%)	3 (25%)
Pre-OIT	Anaphylaxis	49 (43%)	10 (50%)	5 (42%)
	Injectable adrenaline	21 (19%)	4 (20%)	1 (8%)
	Emergency room	41 (36%)	8 (40%)	4 (33%)
	Hospitalization	9 (8%)	3 (15%)	1 (8%)
	SPT wheal size (mm)	8 (6-10)	8 (7-10)	10 (8-12)
Buildup	SHTD (mg)	25 (8.8-150)	7.5 (5-14.4) ^a	10 (4-30)
	Reactions-hospital (#)	1 (1-2)	2.5 (1-3.8) ^a	1.5 (1-2.8)
	Adrenaline-hospital	13 (12%)	2 (10%)	3 (25%)
	Reactions-home (#)	1 (0-3)	7.5 (0-21) ^a	6 (1-14.5) ^a
	Adrenaline-home	10 (9%)	9 (45%) ^b	2 (17%)
	NAN GI symptoms ^c	4 (4%)	2 (10%)	3 (25%) ^d

SHTD, single highest tolerated dose; NAN, non-anaphylactic.

Categorical variables are presented as mean (%). Continuous variables had abnormal distribution and are presented as median (interquartile range).

^aSignificant difference from group 1 after applying Bonferroni correction.

^bSignificant difference from group 1 and group 3 applying Bonferroni correction.

^cRefers to gastrointestinal symptoms unrelated to the consumption of the daily dose.

^dSignificant difference compared to patients who continued treatment.

reactions requiring adrenaline at clinic during up-dosing (28.6% vs 9.7%, $P = .026$), lower SHTD (mean 27 ± 64 mg vs 94 ± 152 mg, $P = .001$), longer treatment (13.5 ± 6.7 months vs 8.4 ± 6.3 months, $P = .001$), and lower rate of reaching full desensitization (47.6% vs 83.1%, $P < .001$).

3.2 | Long-term follow-up

Of the 133 fully or partially desensitized patients, 130 (111 full and 19 partial, 97.7%) were already >6 months on maintenance at the time of the study and were available for analysis (Figure 1). Three patients were not available despite repeated attempts in various ways. Forty-nine (38%) patients described occasional short (<7) days breaks, and 15 (12%) had >7 day breaks in maintenance dose consumption but subsequently continued treatment without reactions. Only 12 patients experienced objective reactions, and 2 patients (1.6%) required injectable adrenaline during this part of the treatment. Non-anaphylactic gastrointestinal symptoms were not reported during maintenance. Median length of follow-up for those continuing consumption of peanut was 18 months (range, 6-75 months). Of the 130 patients followed, 17 (13%), 14 with full and 3 with partial desensitization, discontinued treatment after a median of 4 months (range, 1 week-21 months). Reasons for discontinuing treatment were food aversion in 13 patients, difficulty in incorporating the dose with daily activities in 3, and complaints of heartburn (normal gastroscopy) in one. Information regarding long-term follow-up of patients who stopped maintenance after reaching

full desensitization is presented in Table S4. Of the 97 patients who continued daily peanut consumption, 33 were already >2 years after reaching maintenance. Patients followed up for >2 years were comparable to those followed <2 years in skin sensitivity, QOL perception, and reactions experienced during maintenance. These patients had more short breaks (<7 days duration) during treatment as compared to those followed up for <2 years (30% vs 8%, $P = .006$). This could potentially reflect their increased confidence or alternatively, since most of them were required to consume a high daily dose (72.7% vs 0, $P < .001$) compliance was difficult.

3.3 | Factors affecting discontinuation of treatment after reaching full desensitization

Discontinuing peanut consumption after reaching full dose was associated with more adrenaline-treated reactions both before OIT and during its buildup phase but not after reaching maintenance (Table 2). Patients who discontinued treatment were more likely to consume a high (3000 mg) maintenance dose ($P < .001$). Peanut SPT wheal diameter decreased by 50% and skin sensitivity decreased significantly ($P = .03$) in patients who continued treatment but did not significantly change in those who stopped (Table 2). On multivariate analysis, a low maintenance dosing (1200 mg) regimen (OR 12.5, 95% CI 2.9-52.8, $P = .001$) and not requiring adrenaline at home during the buildup phase of OIT (OR 7.8, 95% CI 1.4-43.5, $P = .02$) significantly predicted a patient's likelihood to continue peanut consumption during maintenance.

TABLE 2 Comparison of patients based on long-term outcome

Period	Parameter	Continued treatment (n = 97)	Stopped treatment (n = 14)	P value
Demographics	Male gender	62 (64%)	8 (57%)	.77
	Age (y)	6.1 (4.5-8)	6.7 (4.5-12)	.41
	HDM sensitivity	71 (74%)	10 (71.4%)	.53
	Asthma	38 (39%)	6 (43%)	.78
	Other food allergies	47 (49%)	3 (21%)	.08
pre-OIT	Anaphylaxis	38 (39%)	10 (71%)	.04
	Injectable adrenaline	15 (16%)	6 (43%)	.025
	Emergency room	35 (36%)	6 (43%)	.77
	Hospitalization	8 (8%)	1 (7%)	1.0
	SPT wheal size (mm)	8 (6-10)	8 (5-13.5)	.62
	Histamine wheal size (mm)	3 (2-5)	3 (1-5)	.93
	Median SPT (C_{ha}) ^a	0.01 (0-0.1)	0 (0-0.06)	.2
Buildup	Starting dose (mg)	25 (10-125)	35 (6.9-300)	.55
	Reactions-hospital (#) ^b	2 (1-2)	2 (1-3.3)	.33
	Adrenaline-hospital	9 (9%)	4 (29%)	.06
	Reactions-home (#) ^b	1 (0-3)	0.5 (0.5-3)	.58
	Adrenaline-home	6 (6%)	4 (29%)	.022
	Length (m)	8.8 (4.3-12.8)	6.8 (2.6-13.7)	.46
Maintenance	Low maintenance dose	73 (75%)	3 (21%)	<.001
	Reactions (#)	0 (0-0)	0 (0-0)	.4
	Adrenaline	2 (2.1%)	0	1.0
	SPT wheal size (mm) ^c	4 (3-7)	8 (7-12)	.003
	SPT wheal change ^d	0.54 (0.32-0.75)	1.0 (0.6-1.9)	.015

^aCalculated per ref 30.^bCategorical variables are presented as mean (%). Continuous variables had abnormal distribution and are presented as median (interquartile range).^cAvailable for 85 patients in those who continued and 7 in those who stopped.^dCalculated as SPT wheal size at follow-up/SPT wheal size at enrollment
Significant values are presented in bold print.

The 36 patients who continued daily consumption of 3000 mg protein (higher dose group) and the 76 consuming 1200 mg (low-dose group) did not differ in pre-OIT characteristics or in the course of OIT (data not shown). 31.4% of patients in the high-dose group discontinued treatment compared to only 3.9% of those in the low-dose group ($P = .001$; Figure 2A). A Kaplan-Meier curve with log-rank test analysis demonstrates that the time to treatment cessation in the high-dose group was significantly shorter (Figure 3). Patients who liked or were indifferent to peanuts continued treatment, while patients with significant food aversion, despite having comparable reaction severity before and during OIT, were more likely to discontinue treatment (Figure 2B).

3.4 | Efficacy of low maintenance dosing

Sixty-six patients of the fully desensitized low-dose group were challenged to 3000 mg peanut protein and 63 (95.5%) passed. Of the 3 who failed, 2 did not follow our recommendation and consumed less than 1200 mg. A single patient, who was consuming 1200 mg daily, reacted and required injectable adrenaline. All patients in the high-dose group (3000 mg) who continued regular consumption and arrived for follow-up ($n = 22$) passed a challenge to 3000 mg. Of the partially desensitized group, consuming 300-2400 mg, 3 discontinued treatment and 10 patients were challenged to 3000 mg.

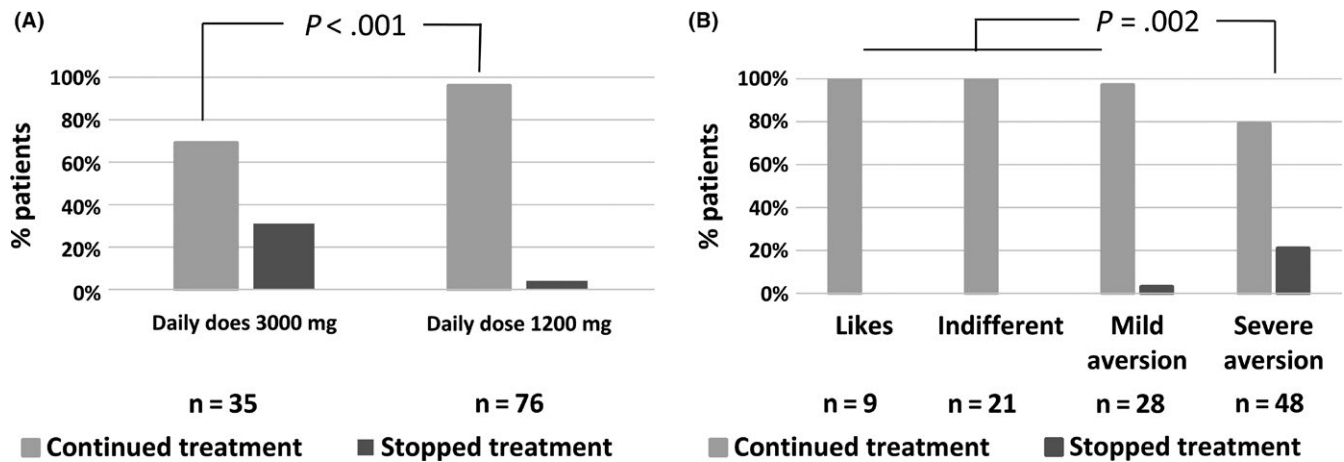


FIGURE 2 Attitude to peanuts and treatment compliance. A comparison of the % of patients compliant with their maintenance treatment regimen based on the dose taken (A) and based on their respective attitudes toward peanuts consumption (B)

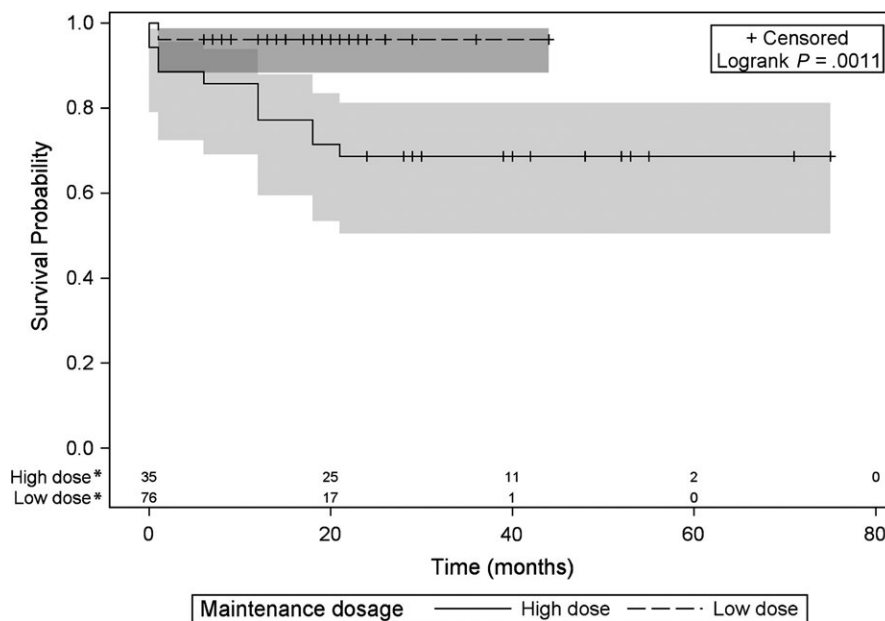


FIGURE 3 Time to discontinuing treatment based on dose taken. A Kaplan-Meier curve demonstrating the time to discontinued maintenance consumption based on the dose (high vs low) taken in patients reaching 3000 mg. Vertical lines represent censored patients. *Represents number of patients followed at each time point for each dose, respectively

All 10 patients (8 consuming ≤ 1200 mg) passed the OFC. Thus, 123 patients (113 initially and 10 after long-term maintenance, shaded boxes in Figure 1) of the 145 enrolled (84.8%) were able to reach full desensitization. After long-term follow-up, 61.1% of patients initially tolerating < 5 mg achieved full desensitization compared to 88.2% of patients who tolerated ≥ 5 mg ($P = .006$, Figure 4). Of the 142 patients followed, 113 (79.6%, rectangles in Figure 2) continued regular peanut consumption long-term.

4 | DISCUSSION

The current study provides data on “real-life” experience with OIT in a large group of peanut-allergic patients. We found that peanut OIT is effective in most patients, including those with a very low

threshold, prior anaphylactic reactions, or the presence of asthma. We show that difficulty in taking the recommended daily dose is the main obstacle leading to cessation of treatment, both during buildup and after reaching maintenance phase of treatment. Difficulties during maintenance were almost completely overcome by reduction in the required dose while desensitization efficacy remained unchanged.

Peanut allergy affects a growing number of patients, posing a risk of life-threatening reactions upon accidental exposure and impairing quality of life.²⁻⁵ Unlike milk and egg, most peanut-allergic patients will retain their allergy overtime.²⁵ Previous randomized controlled studies have shown that peanut OIT is effective, with 61% to 90% achieving full desensitization (for review see 6). However, some studies excluded “high risk” patients, such as those unable to tolerate at least 1.5 mg of peanut protein.¹² We demonstrate the high efficacy of peanut OIT in

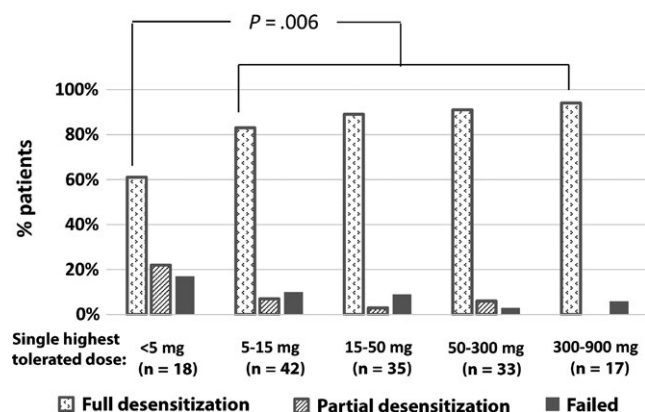


FIGURE 4 Treatment outcome according to the maximal tolerated starting dose. Treatment outcome at the end of long-term follow-up for patients reaching full (3000 mg) or partial (300 to <3000 mg) desensitization and those who failed is shown for groups categorized according to the highest single tolerated dose at initial escalation week

a “real-life” setting and over a long maintenance period. Our findings add support to the recent EAACI recommendation that OIT for peanut should be recommended in clinical practice.⁸ The fact that patients aged >11 years had similar outcome as younger children is important given that these age groups are at increased risk for near-fatal and fatal reactions.³

Some of the main obstacles in food OIT are adverse reactions experienced during treatment.^{9,26,27} Although most reactions in our study were mild (grade 1 or 2), 21 patients (14.4%) had home reactions requiring injectable adrenaline, during the buildup phase. While this is a significant number, adrenaline use is encouraged in our OIT program and this number might reflect overtreatment. Importantly, most patients who required adrenaline continued treatment and were able to achieve full or partial desensitization, although their course was more difficult. This finding does emphasize, however, the importance of performing OIT only in qualified centers with the expertise of providing this form of treatment. Our unique web-based reporting system and the availability of on-call physician 24/7 provide additional support to the patients and improve safety.²¹

Fourteen patients (12.6%) in our cohort discontinued treatment after reaching full desensitization. Cessation of treatment was not due to adverse reactions during maintenance, as reported by others,⁷ but primarily due to an aversion to peanuts. Following reduction in the maintenance dose to 1200 mg peanut protein the rate of discontinuing treatment dropped markedly. Adrenaline-treated reactions at home during buildup were also associated with treatment cessation, perhaps by contributing to anxiety and increasing food aversion.

Nearly all patients consuming 1200 mg daily retained their full desensitization on follow-up. Moreover, patients who were partially desensitized initially and were consuming low daily doses were also fully desensitized on follow-up. Several previous studies used low-dose maintenance during peanut OIT but subsequently challenged patients to 1400 mg only or to repeated doses of 830 mg which are

not the typical end-points for peanut OFC.^{27,28} Our study provides evidence that low-dose maintenance is effective in preserving full desensitization. While some patients consuming <1200 mg protein also passed an OFC to 3000 mg, as described by others,²⁹ the rate of failure in this group was higher. Future studies are needed to examine whether longer duration of maintenance would enable further reduction in the daily dose.

Being a clinical “real-life” description, no control group was used in this study. Peanut OIT has already been shown to be effective in randomized controlled trials⁶ and for the goals of this study, to examine how OIT can be implemented in clinical practice, the clinical character of our treatment program was advantageous. Furthermore, the observation that patients who stopped maintenance treatment in our study did not have reductions in SPT and greater than 90% were reactive upon accidental exposure or re-challenge negates the notion that these patients would spontaneously recover.

In summary, this study presents promising short- and long-term results for peanut OIT under “real-life” conditions in a large group of patients. The findings that most patients, including highly reactive ones and asthmatics, have high success rates and that adverse reactions, after reaching maintenance, are relatively few is encouraging. Still, it should be emphasized that severe reactions requiring injectable adrenaline occur and that the treatment should be performed only in food allergy specialized centers. As patients will likely be required to consume peanuts regularly long after reaching full desensitization, a low maintenance dose could offer the advantage of better compliance without impairing treatment efficacy.

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CONFLICT OF INTEREST

Liat Nachshon, Michael R Goldberg, Yitzhak Katz, Michael B Levy, and Arnon Elizur do not have any conflict of interests to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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SUPPLEMENTARY MATERIAL

Patients:

Inclusion criteria included a clinical history of an immediate reaction (cutaneous, gastrointestinal, respiratory and/or systemic symptoms occurring within 2 hours) to peanut following accidental ingestion in the past year or a positive open label oral food challenge (OFC) together with evidence for peanut sensitization based on a positive skin prick test (SPT) and/or specific serum IgE (>0.35 k U/L). Patients with uncontrolled asthma, a medical contra-indication to receive adrenaline, or inability to adhere to protocol were excluded. A comprehensive medical history was obtained from each patient/parent including the occurrence of previous reactions, treatments provided including the use of injectable adrenaline, emergency department visits and hospital admissions. Patients/parents were asked about other atopic diseases including additional food allergies. SPT to peanuts (1:10 w/v; ALK-Abello, Port Washington, New York) were performed on the volar surface of the forearm of all patients with single peak lancets (Heinz Herenz, Hamburg, Germany) and mean wheal diameter was measured after 20 minutes. Histamine 1 mg/mL (ALK-Abello) and saline were used as positive and negative controls. A positive SPT was defined as a wheal diameter ≥ 3 mm over the negative control. C_{ha} was calculated before and after OIT (30). Informed parental (for patients $<$ age 18 years) or patient (for patients $\geq$ age 18 years) consent was obtained from all participants. Institutional Review Board Committee approval was obtained for the publication of patient data.

Peanut dose preparation: Peanut doses up to 300 mg were prepared from peanut flour (12% fat, Byrd Mill, Ashland Va.) which received no special standardization other than being placed into solution. Briefly, 80 gram of Light Roast peanut flour was placed in a total of 400 ml of mineral water pH 7.9 and blended at high speed for 15 minutes. Blending was repeated three

times with fifteen minute intervals between each cycle to allow the mixture to cool. The peanut suspension did not reach $> 45^{\circ}\text{C}$ during blending cycles. The peanut suspension (100 mg/ml) was then used or frozen in aliquots at -20°C for future use. Peanut doses of ≥ 300 mg were given as regular peanuts.

Peanut OIT Protocol: The initial days of the first dose-escalation round served as an OFC up to 3000 mg peanut protein (Table 1s). Patients who did not react were classified as non-allergic and excluded. If a reaction occurred, the following days served to identify the single highest tolerated dose (SHTD), defined as the maximal amount of peanut protein the patients could safely consume (previously defined maximal individualized tolerated dose (MITD) (9)). 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 two 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 and patients were instructed to send a daily report of their home dose consumption, including any experienced reactions and any treatments provided, via e-mail or a web-based reporting system (21). 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 consumption at home. The 3rd cycle consisted of 3 days with a goal of 3-fold dose

increase. The 4th and 5th 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 3000 mg peanut protein was achieved

Table 1s: First week peanut oral immunotherapy protocol

	Dose	Amount (mg peanut protein)	Interval (min)
Day 1	1	0.1	0
	2	0.2	10
	3	0.5	10
	4	1.25	20
	5	5	20
	6	10	30
	7	15	30
	8	25	30
	9	50	45
	10	50 ^a	90
	--	Observation	90
Day 2	1	50	0
	2	100	20
	3	150	30
	4	200	30
	5	250	30
	6	300	30
	7	300	90
	8	900	90
	9	3000	90
	--	Observation	90
Day 3	1	A dose below the MITD	0
	2	MITD	90
	3	MITD	90
	--	Observation	90
Day 4	1	MITD	0
	2	MITD	90
	--	Observation	90

^a 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.

Table 2s: Characteristics of the study population

	Parameter	Frequency [*]
Demographics	Male gender	89 (62%)
	Age (y)	5.8 (4.5 – 7.8)
	Asthma	56 (39%)
Other food allergies	Tree-nuts	44
	Sesame	21
	Milk	9
	Egg	8
Pre-OIT	Anaphylaxis	64 (44%)
	Injectable adrenaline	26 (18%)
	Emergency room	53 (37%)
	Hospitalization	13 (9%)
	SPT wheal size (mm)	8 (6.3 – 10)
OIT treatment	Starting dose (mg)	20 (7.5 – 100)
	Treatment duration (m)	8.7 (3.8 – 12.8)

^{*} Categorical variables are presented as mean (%). Continuous variables had abnormal distribution and are presented as

median (**interquartile range**)

Table 3s: Induction and home adverse reactions* during OIT build-up phase

Phase	Adverse reactions	Number (percentage)
Induction doses	Perioral	6 (4%)
	Skin	60 (41%)
	Upper respiratory	59 (41%)
	Eye	13 (9%)
	Lower respiratory	21 (15%)
	Gastro-intestinal	105 (72%)
	≥2 systems	64 (44%)
	Grade 1	75 (52%)
	Grade 2	105 (72%)
	Adrenaline	18 (12%)
Home doses	No reaction**	58 (40%)
	A single reaction	25 (17%)
	2-4 reactions	29 (20%)
	≥5 reactions	33 (23%)
	Adrenaline	21 (15%)
	Non-anaphylactic symptoms	9 (6%)

* Induction adverse reactions are based on the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (29)

** Reflects no anaphylactic or non-anaphylactic reactions

Table 4s. Follow-up of Patients who stopped OIT after reaching full desensitization

Patient	Length (months)	Reason	Subsequent reactions	OFC	Resumed OIT*
1	18	GERD**	No	Positive	No
2	6	Refusal to continue	No	Positive	No
3	1	Refusal to continue	No	Positive	No
4	0.25	Refusal to continue	No	Positive	Yes
5	0.25	Refusal to continue	No	Refused	No
6	0.25	Refusal to continue	No	Refused	No
7	21	Refusal to continue	No	Negative	No
8	18	Refusal to continue	No	Positive	No
9	12	Technical†	Yes	Not done	No
10	12	Refusal to continue	Yes	Not done	Yes
11	12	Technical	Yes	Not done	No
12	0.25	Refusal to continue	Yes	Not done	No
13	1	Refusal to continue	Yes	Not done	No
14	1	Refusal to continue	Yes	Not done	Yes

*The 3 patients who resumed OIT were desensitized to 3000 mg

** GERD- Gastro-Esophageal Reflux Disease - A 32-year-old women, stopped OIT due to complaints of "heartburn". Upon evaluation, her gastroscopy was normal.

† Refers to 2 teenage patients who discontinued their daily dose because of a long travel away from home on their own