

ORIGINAL ARTICLE

Clinical Allergy

Individually dosed omalizumab facilitates peanut oral immunotherapy in peanut allergic adolescents

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Abstract

Background: Peanut oral immunotherapy (pOIT) has showed good short-term outcomes, but allergic reactions may prevent effective up-dosing and is a major cause of stopping OIT. In placebo-controlled trials, omalizumab has been shown to facilitate allergen immunotherapy and increase tolerance to peanut.

Objective: We hypothesized that by combining omalizumab with pOIT, and monitor treatment effects with basophil allergen threshold sensitivity tests (CD-sens), peanut allergic patients could safely initiate pOIT and thereafter slowly withdraw omalizumab.

Methods: This is the 2nd part of a one-armed open phase-2 study where peanut allergic adolescents (n = 23) started pOIT after an individualized omalizumab treatment. The pOIT dose was increased from 280 to 2800 mg peanut protein in 8 weeks followed by an individualized step-wise withdrawal of omalizumab, based on clinical symptoms and CD-sens levels. pOIT continued for 12 weeks followed by an open peanut challenge. Peanut CD-sens and allergen-binding activity (ABA) and IgE-ab, IgG-ab and IgG4-ab to peanut and its components were measured during the study. **Results:** All 23 patients successfully reached the 2800 mg maintenance dose. Moderate/systemic allergic reactions were rare while receiving full-dose omalizumab. Eleven of 23 (48%) successfully continued with pOIT after omalizumab was stopped. Compared to treatment failures, median baseline IgE-ab to peanut components Ara h 1-3 and CD-sens to peanut were significantly lower among successfully treated patients and IgG4-ab to peanut, Ara h 2 and 6 increased significantly more during treatment.

Conclusions and clinical relevance: This study indicates that omalizumab is an effective adjunctive therapy for initiation and rapid up-dosing of pOIT; however, adverse events from pOIT become more frequent as omalizumab doses are decreased.

Clinical trials registration: ClinicalTrials.gov; NCT02402231. EudraCT; 2012-005625-78.

KEYWORDS

anaphylaxis, basophil, food allergy, omalizumab, oral immunotherapy, paediatrics

Brandström, Vetander, Nopp, and Nilsson contributed equally to this work.

1 | INTRODUCTION

Peanut allergy is the main cause of anaphylaxis among children,¹ and the prevalence is increasing.²⁻⁴ In 2017, the European Academy of Allergy & Clinical Immunology (EAACI) published recommendations for allergen immunotherapy (AI) for IgE-mediated food allergy,⁵ the first disease-modifying treatment for peanut allergy.

Sub-cutaneous immunotherapy (SCIT) has been used for over a century⁶ for treatment of pollen allergy and later, insect venom allergy. It is safe, efficacious and cost-beneficial.⁷⁻¹⁰ SCIT was tried for peanut allergy but high rates of adverse events (AE) deterred from further use.^{11,12} Instead, other routes of administration (oral,¹³ sublingual,¹⁴ epicutaneous¹⁵ and rectal¹⁶) have been tried with varying results. Oral immunotherapy (OIT) has good short-term outcomes; in peanut oral immunotherapy (pOIT), most participants become desensitized and tolerant to gram doses.^{17,18} However, some patients cannot tolerate even the lowest doses. Most subjects experience AEs; although mostly mild, severe reactions occur, thus preventing patients from reaching effective doses and forcing patients to stop treatment.^{5,19} Also, it seems that OIT is less effective in patients with severe allergy and high IgE-ab levels.^{17,19,20}

Omalizumab, a humanized anti-IgE antibody mainly used in allergic asthma, decreased peanut allergic subjects' sensitivity to peanut.^{21,22} Omalizumab has been shown to facilitate initiation of OIT, reduce AEs but no significant enhanced tolerance has been observed post-omalizumab discontinuation.^{18,20,23}

We have successfully used the basophil activation test, CD-sens, to monitor OIT, SCIT and omalizumab treatment.²⁴⁻²⁶ SCIT and OIT stimulate production of allergen blocking factors, including IgG4-ab.^{19,27} These factors exert an allergen-binding activity (ABA).²⁵ If ABA is present, more allergen is needed to trigger basophils and the CD-sens will be lower. ABA is induced by SCIT^{25,27} but not by omalizumab.²⁸

Our primary aim was to evaluate safety and clinical outcome of a CD-sens monitored combined therapy of omalizumab and pOIT, in peanut allergic adolescents. We also followed IgG/IgG4-ab and ABA to find prognostic markers for pOIT outcome.

2 | METHODS

2.1 | Study design

This is the 2nd part of a one-armed phase-2 study of omalizumab-facilitated peanut OIT. Briefly, in the first part²⁶ 23 peanut allergic adolescents, with positive peanut CD-sens, were treated with omalizumab at the recommended doses for allergic asthma for 8 weeks, and the omalizumab doses were then increased, if needed, until CD-sens to peanut was suppressed. Thereafter, a peanut challenge ensued, where as previously reported, all 23 included patients could ingest a minimum of 840 mg of peanut protein (median 2800 mg).²⁶ Inclusion criteria for this study were severe peanut allergy with a history of systemic reactions

(convincing history of anaphylaxis or anaphylaxis or symptoms indicating an impending anaphylaxis at food challenge), IgE sensitization, positive skin prick test (SPT) and CD-sens to peanut and after individualized omalizumab treatment for 8-32 weeks tolerating >1 g of peanut (280 mg peanut protein) at the open challenge marking the end of the first part of this two-step study.²⁶ As a control, subjects also had an allergy to pollen or pets with clinical symptoms, positive SPT, IgE sensitization and positive CD-sens. Exclusion criteria were previous omalizumab treatment or immunotherapy for peanut/control allergen and chronic non-atopic co-morbidities.

The study was approved by the ethics committee in Stockholm; 2013/827-31/3, Swedish Drug Agency; 5.1-2013-46183 and registered at EudraCT; 2012-005625-78, ClinicalTrials.gov; NCT02402231. All patients and caregivers gave their written informed consent.

2.1.1 | Up-dosing phase

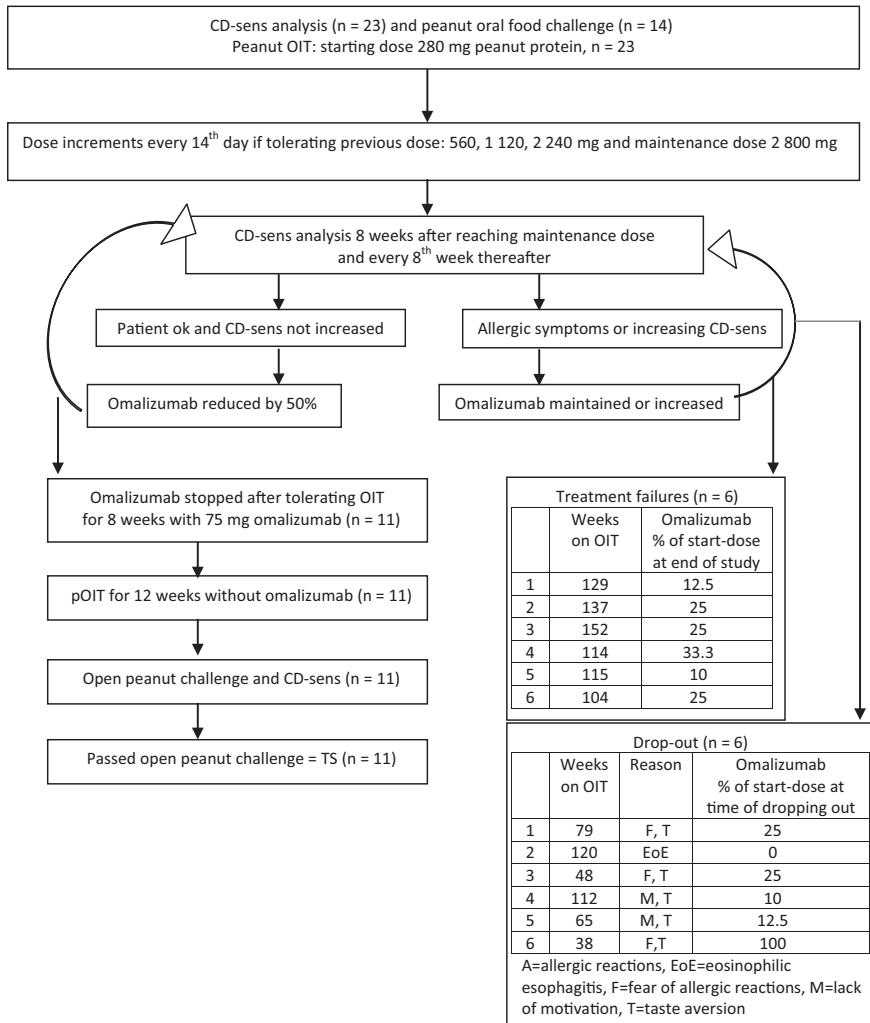
POIT under omalizumab protection started with 280 mg of peanut protein (Figure 1). Doses were increased every 2 weeks if subjects had no/only mild subjective symptoms (like mild oral pruritus or mild self-resolving abdominal pain/discomfort) until reaching the 2800 mg maintenance dose. Daily OIT doses were taken at home. Participants were instructed to not exercise for 2 hours after intake, lower dose when having mild infections, temporarily pause OIT if having fever or gastroenteritis, always carry adrenaline auto-injectors and contact the study centre if they had allergic symptoms. Consultations with study physician were scheduled every 2nd to 4th week; besides participants were contacted weekly and asked about compliance and allergic symptoms.

2.1.2 | Maintenance phase

Eight weeks into maintenance phase peanut CD-sens was measured. If the subject had no or mild subjective symptoms, CD-sens was analysed; and if suppressed (=0 or non-calculable), omalizumab was reduced with 50% otherwise the same dose was given for 8 more weeks. If CD-sens, after 8 more weeks, had decreased and the patient had no or only mild symptoms (see above) the omalizumab dose was also reduced. The procedure was repeated every 8th week. For subjects having systemic reactions, increased omalizumab or temporarily lowered pOIT doses were considered.

2.1.3 | Final phase

Omalizumab was stopped if the subject, after 8 weeks on 75 mg omalizumab, was asymptomatic and CD-sens was suppressed, or after 16 weeks if CD-sens was not completely suppressed but did not increase between week 8-16. POIT was then continued for 12 weeks followed by an in-hospital single-dose peanut challenge with the patient's current OIT dose followed by 2 hours observation time. Subjects passing this challenge were defined as treatment successes (TS). Treatment failure (TF) was evaluated in October



2017 (4 years after study start) and defined as subject not able to discontinue omalizumab treatment with a minimum of 2.5 years of treatment.

2.2 | Immunological assessments

2.2.1 | Basophil analyses

Basophils, from peripheral blood, were quantified and stimulated with an in-house peanut extract (final concentration 0.83-2500 ng/mL). Commercial extracts to airborne allergens; birch, timothy, cat, dog and horse (Aquagen, ALK) were used for control allergens (final concentration: 5-5000 SQU/mL). To differentiate the basophils from the leucocyte population, they were stained for CD203c. To detect activated basophils, the cells were stained for CD63 (Immunotech) followed by analysis in a Navios flow cytometer (Beckman Coulter Inc).

Cut-off determining a positive test was set to 5% of CD63-positive basophils. Patients, whose basophils, after stimulation with the positive control (anti-FcεRI) responded with less than 5% CD63 up-regulation, were regarded as non-responders. Individuals with a response between 5% and 16% were classified as low responders.

The cut-off of 16% was calculated (mean 76%-3 SD) from the positive controls of an in-house (material of 264 allergic children and adults).²⁹ Basophil activation cannot be used to evaluate allergen response among non- and low responders.

Basophil reactivity was measured as the maximal percentage of CD63-positive basophils.³⁰

To determine the basophil allergen threshold sensitivity, CD-sens, the eliciting allergen concentration giving 50% (EC50) of maximal CD63% up-regulation of the dose-response curve, was calculated. CD-sens definition: the inverted value for EC50 multiplied by 100.³¹

When basophils react only at the highest allergen concentration, a CD-sens value cannot be calculated, nor can the test be ruled as negative. In this study, a positive, non-calculable CD-sens value was regarded as "favourable."²⁶

CD-sens was also performed in a serum-depleted 'washed' sample. The ratio between washed CD-sens/whole blood CD-sens was calculated and defined as allergen-binding activity (ABA), a measure of the serum's ability to reduce basophil sensitivity to allergen stimulation.³¹

The number of IgE and FcεRI per basophil was calculated using a FITC-conjugated antibody to IgE (Cedarlane) or FcεRI (eBioscience) and compared to a standard curve of Calibration Beads (DakoCytomation).³²

2.2.2 | Skin prick test

Skin prick test (SPT) to peanut and control allergens was performed at baseline (all) and final visit (TS) using allergen extracts, positive control (histamine) and negative control (diluent) (Soluprick, ALK).

2.2.3 | Serological analyses

Serum (total) IgE, IgE-ab to peanut, Ara h 1-3, 6, 8-9 and control allergen were analysed at baseline and final visit. Since omalizumab interferes with IgE, no IgE-analyses were performed during omalizumab treatment.

IgG-ab and IgG4-ab to peanut, Ara h 2, Ara h 6 and control allergen were analysed at baseline, OIT-start, 8 weeks into maintenance phase and final visit.

ImmunoCAP® (Thermo Fisher Scientific) was used for serological analyses.

2.2.4 | Adverse events and definition of systemic reactions

Patients reported adverse events (AE) by phone and/or at visits. Frequencies of specific symptoms apart from mild self-resolving abdominal pain, mild emesis and oral pruritus were recorded. In case of emergency visits, medical records were independently reviewed by two physicians (JB, MV). Systemic allergic reactions were categorized as follows:

Mild systemic reaction: involvement of ≥ 2 organ systems, not fulfilling the WAO anaphylaxis-criteria.³³

Moderate systemic reaction: involvement of ≥ 2 organ systems fulfilling the WAO criteria for anaphylaxis and criteria for grade 1-2 anaphylaxis according to Muraro et al³⁴

Severe systemic reaction: involvement of ≥ 2 organ systems fulfilling the WAO criteria for anaphylaxis and grade 3 anaphylaxis according to Muraro et al³⁴

2.3 | Statistical analyses

Binary variables are presented as proportions and continuous variables as medians (25th-75th percentiles) if not stated differently. Patient characteristics, laboratory data and AEs were compared between treatment successes (TS), treatment failures (TF) and dropouts using Kruskal-Wallis test and pairwise between groups using Fisher's exact test or Mann-Whitney U test. Page's test was used for trends and signed-rank test for paired data. Spearman's test was used for calculating correlations. No multiple analyses correction was performed. *P*-values < .05 were considered significant.

3 | RESULTS

3.1 | Patient characteristics

The patients were 12-19 years old (median 17), and 70% were females. All subjects were peanut-sensitized; median IgE-ab 86 kU_A/L

(25th-75th percentile 48-220) and Ara h 2; 58 kU_A/L (26-78), positive CD-sens to peanut 0.75 (0.44-20.5) and allergic to pollen and/or pets. Allergic conjunctivitis was the most frequent atopic manifestation (91%) followed by asthma and rhinitis (87%) (Table 1).

3.2 | Clinical outcomes

The primary end-point, pOIT with a daily dose of 2800 mg of peanut protein for 12 weeks after discontinuing omalizumab followed by a negative open challenge with 2800 mg, was met by 9 subjects (39%). Additionally, two subjects completed the study with a reduced pOIT dose (1120 and 700 mg peanut protein), and their lower pOIT doses were not due to allergic symptoms but due to a taste aversion to peanut. These 11 subjects (48%) are referred to as treatment successes (TS). Six subjects withdrew from the study (dropouts). The remaining six subjects, not able to discontinue omalizumab, were considered treatment failures (TF). Their median omalizumab dose at the study's end was 188 mg (min-max 75-300 mg).

All 23 subjects reached the 2800 mg maintenance dose in a median time of 10 weeks with significant differences between TS, dropout and TF groups; 8, 11.5 and 14 weeks, respectively (*P* = .012).

Median pOIT duration in TS was 83 weeks (min-max 48-156) and in TF 139 weeks (min-max 115-166) (*P* = .035) (Figure 1).

3.2.1 | Characterization of dropouts

Median time of study withdrawal was 72 weeks into pOIT (min-max 38-120). Dropouts (*n* = 6) did not differ from the TS or TF in terms of baseline characteristics, their median IgE-abs, CD-sens and SPT were in between the medians for the TS and TF groups. Frequencies of adverse events were also, in general, not significantly different from the TS and TF groups with two exceptions: dropouts had less subjective throat tightness than TF (*P* = .007) and more frequently moderate systemic reactions than TS, 0.16% vs 0.02% (*P* = .046) (Table 1, Table S1). Three subjects stated a combination of fear of having reactions and taste aversion for peanuts while two stated lack of motivation and taste aversion as reasons for dropping out. One patient discontinued the study after being diagnosed with eosinophilic esophagitis (EoE).

3.2.2 | Adverse events (AEs)

Mild oropharyngeal and mild abdominal symptoms were reported by 82% and 64%, respectively, in TS and by 100% and 83%, respectively, in TF. Frequencies of other symptoms are displayed in Table 2.

Among all subjects, 43 systemic reactions, in 16 095 doses (0.3%), occurred: 20 mild, 22 moderate and one severe (Figure 2 and Table S1). All but three moderate reactions were classified as anaphylaxis based on skin/mucosal symptoms in combination with subjective breathing difficulties. Only 4/43 systemic reactions occurred while the patient received full dose of omalizumab (two during pOIT up-dosing and two after reaching maintenance dose) in which co-factors were noted in two cases (exercise, infection). In 55% of TS and 100% of TF ≥ 1 , systemic reaction was experienced. One patient

TABLE 1 Patient characteristics, serology, CD-sens and Skin Prick Test at baseline

	Total n = 23	Treatment success n = 11	Treatment Failure n = 6	P	Drop-out n = 6
Patient characteristics; n (%)					
Gender, female	16 (70)	9 (82%)	3 (50)	.28	4 (67)
Rhinitis	20 (87)	8 (73)	6 (100)	.51	6 (100)
Asthma	20 (87)	10 (91%)	5 (83%)	1.0	5 (83)
Conjunctivitis	21 (91)	11 (100)	5 (83%)	.35	5 (83)
Eczema	6 (26)	3 (27)	1 (17)	1.0	2 (33)
Allergic to pets	18 (78)	10 (91)	3 (50)	.10	5 (83)
Allergic to tree/grass pollen	20 (87)	8 (73)	6 (100)	.51	6 (100)
>2 atopic manifestations	15 (65)	7 (64)	3 (50)	.64	5 (83)
Increased pre-OIT omalizumab dose	15 (65)	6 (55)	5 (83)	.25	4 (67)
Age; years, median (range)	17 (12-19)	16 (12-18)	17 (13-18)	.35	17(15-18)
Sampson score(1-5) ^{26,47} of severity at OFC or anaphylaxis prior to inclusion. Mean (min-max)	3.8 (3-4)	3.7 (3-4)	3.8 (3-4)	1.0	3.8 (3-4)
IgE-ab; kU _A /l, median (25th-75th percentile)					
Total serum IgE	470 (230-680)	410 (160-680)	505 (440-680)		400 (140-630)
Peanut	86 (48-220)	52 (41-165)	200 (86-290)	.02	150 (34-250)
Ara h 1	21 (9.2-68)	16 (7.5-24)	53 (21-71)	.02	26 (7.8- 84)
Ara h 2	58 (26-78)	30 (24-66)	72 (58-185)	.03	50 (32-97)
Ara h 3	3.4 (2.1-14)	2.3 (1-5.2)	13 (9.8-16)	<.01	2.8 (1.9- 16)*
Sum of Ara h 1 + 2+3	103 (53-136)	57 (37-107)	136 (105-295)	.02	94 (40-190)
Ara h 6	49 (26-66)	39 (23-66)	60 (49-140)	.25	n/a
Ara h 8	2.3 (0.61-6.6)	0.98 (0.22-6.6)	4.6 (2.4-5.5)	.48	1.45 (0.8-12)
Ara h 9	0.01 (0.01-0.28)	0.01 (0.01-0.09)	0.01 (0.01-0.1)	.40	0.01 (0.01-0.01)
Ara h 2/total IgE	0.14 (0.11-0.20)	0.1 (0.1-0.19)	0.16 (0.12-0.03)	.19	0.16 (0.15-0.25)
CD-sens; median (25th-75th percentile)					
CD-sens	0.8 (0.4-1.9)	0.5 (0.3-1.5)	6.7 (1.5-9.5)	.02	0.9 (0.5-1.6)
CD-sens washed	1.9 (1.5-10)	1.7 (1.3- 6.9)	8.2 (1.8-35)	.10	2.6 (2.2-2.9)
ABA	2.7 (1.7-5.5)	3.8 (2.2-5.9)	1.5 (1.3-3.5)	.10	n/a
Skin Prick Test peanut, mm	10 (9-14)	12 (9-14)	13.5 (10-15)	.41	10 (8-10)
Skin Prick Test control allergen, mm	6 (5-8)	7 (5-10)	6.5 (6-7)	.48	5.5 (4-6)

Note: Data is shown in relation to outcomes: Treatment Success, treatment failure and drop-out. *P*-values column reports comparison of Treatment success (TS) and Treatment failure (TF) with Mann-Whitney U test/ Fischer's exact test. *P*-values for dropouts: Only statistically significant difference when comparing TF and/or TS with dropouts was for Ara h 3. *P*-values <.05 in bold.

Abbreviation: ABA, allergen-binding activity = ratio of washed CD-sens/CD-sens.

**P* = .045 (Kruskal-Wallis test).

alone (TF) accounted for 14 of the 43 systemic reactions. Three of 11 TS and 5/6 of TF were treated with adrenaline, corresponding to a frequency of 0.1% (TS) and 0.2% (TF) of pOIT doses. In the TF group, 22/27 systemic reactions occurred when omalizumab had been decreased by ≥75%. The single severe systemic reaction occurred after omalizumab had recently been discontinued; omalizumab (75 mg) was restarted and successfully discontinued 7 months later. Although frequencies of allergic symptoms, systemic reactions, adrenaline injections and emergency department visits were generally higher in TF compared to TS; they were only significant for moderate systemic

reactions (*P* = .011), adrenaline treatment (*P* = .039), at home-administered adrenaline (*P* = .011) and borderline significant for chest tightness and hospital admission (*P* = .048 for both).

One TS developed epigastralgia 14 months into pOIT; gastro-colonoscopy showed non-eosinophilic esophagitis. Symptoms resolved after omeprazole therapy. Another subject had mild intermittent cough during up-dosing (not correlating to the time of peanut ingestion), the symptoms first disappeared but came back and eventually swallowing difficulties developed. Oesophageal biopsies demonstrated EoE; symptoms resolved completely after stopping pOIT.

3.3 | Immunologic markers

3.3.1 | Baseline data in relation to outcome

Treatment successes had lower median baseline IgE-ab to peanut and components Ara h 1-3 and lower CD-sens to peanut than TF; peanut 52 kU_A/L (41-165) vs 200 kU_A/L (86-290) ($P = .021$), Ara h 2 30 kU_A/L (24-66) vs 72 kU_A/L (58-185) ($P = .034$) and CD-sens 0.52 (0.29-1.5) vs 6.7 (1.5-9.5) ($P = .021$). Similar differences in IgE-ab between TS and TF were seen for Ara h 1 ($P = .016$) and Ara h3 (.009). No significant differences were seen for IgE-ab to Ara h 6, 8-9, control allergen, Ara h 2 IgE-ab/total IgE-ratio or SPT (Table 1).

3.3.2 | IgE and SPT

IgE was not measured during omalizumab treatment. From baseline to final visit, no significant differences were seen: total IgE and IgE-ab to peanut increased slightly while IgE-ab to control allergens decreased marginally (data not shown).

SPT for peanut weal diameter decreased significantly in TS from baseline; 12 mm (9-14) to final visit; 7 mm (3-8) ($P \leq .01$) while SPT to control allergen did not; baseline 7 mm (5-10) and final visit 5 mm (4-9) ($P = .1$).

3.3.3 | IgG and IgG4

Treatment successes had significantly lower baseline IgG4-ab to Ara h 2 and 6 compared to TF (Table 3). IgG-ab and IgG4-ab remained constant from baseline to start of pOIT and hence not affected by omalizumab. From start of pOIT until final visit IgG/IgG4-ab to peanut, Ara h 2 and 6 increased significantly (P for trend $\leq .0001$ for all) (Table 3, Figure 3A,B). At final visit, TS had higher levels of IgG/IgG4 to peanut, Ara h 2 and Ara h 6 than TF in absolute figures but these differences were only significant for Ara h 2 IgG and Ara h 6 IgG4 ($P = .07$ for both). From baseline to final visit; IgG4-ab to peanut, Ara h 2 and 6 had increased 33, 79 and 186-fold, respectively, (TS + TF) and significantly more so in TS; Ara h 2 IgG4-ab median fold increase of 204 (79-354) vs TF 26 (4-51) ($P = .005$) and for Ara h 6; 521 (TS) and 29 (TF) ($P = .0013$). From maintenance phase to final visit IgG4-ab to peanut, Ara h 2 and 6 increased and more so in TS; peanut; 6-fold ($P = .02$), Ara h 2; 6-fold ($P \leq .01$), Ara h 6; 5-fold ($P \leq .01$) while no significant increases were seen in TF; peanut; 1.7-fold ($P = .25$), Ara h 2; 1.3-fold ($P = .35$) and Ara h 6; 1.8-fold ($P = .46$). IgG-ab and IgG4-ab to control allergens remained constant throughout the study (Figure 3C).

3.3.4 | FcεRI and cell-bound IgE

Basophils and cell surface-bound FcεRI and IgE were quantified at baseline, pOIT start, maintenance phase and final visit. Omalizumab suppressed the cell-bound IgE by 98% and the FcεRI by 92% from baseline to pOIT start and thereafter increased as omalizumab

was discontinued. At final visit, FcεRI and cell-bound IgE among TS had increased up to 66% and 80%, respectively, of baseline values (Table 4).

Basophil activation

In the first part of this study,²⁶ we reported that CD-sens to peanut was suppressed in 22/23 patients (the final patient had a CD-sens of 0.13) after the omalizumab pre-treatment. After 8 weeks of pOIT with the 10 g peanut maintenance dose, CD-sens was suppressed in all patients. A small, but borderline significant increase in CD-sens to peanut was seen among treatment successes (TS) from the median at maintenance phase of 0 (0-0) to the final visit (when TS had been off from omalizumab for 12 weeks) median of 0 (0-0.27) ($P \leq .048$). Also, two subjects had become 'non-responders' in CD-sens at this time-point. TF had a more pronounced increase in CD-sens from maintenance phase, when the median was 0 (0-0) to the final visit median of 0.41 (0.14-0.57) ($P = .03$), despite that they were still treated with omalizumab (median dose of 188 mg/4th week). CD-sens to the control allergen was lower at final visit (median 2.5) as compared with baseline values (median 3.8) among TS, but not significantly ($P = .1$). Treatment failures, on the other hand, had significantly lower CD-sens to control allergen at final visit, median 0.3 vs 5.6 at baseline ($P = .03$).

Basophil reactivity to peanut showed a slightly different pattern compared to CD-sens. The reactivity was decreased to 12.5% of the baseline value ($P \leq .001$) during the omalizumab pre-treatment and continued to decrease significantly during the OIT up-dosing phase from 12.5% of baseline value to 2.5% ($P \leq .001$), with no significant differences among the groups. Just like CD-sens, basophil reactivity increased as omalizumab doses were lowered or discontinued but more so in TF reaching 85% (81-89) of baseline levels compared to 30% (16-77) in TS ($P = .04$) (Table 4).

3.3.5 | Allergen-Binding Activity (ABA)

ABA to peanut increased significantly from a baseline median of 3.8 (2.2-5.9) to 49 (9-89) at the final visit in TS ($P \leq .01$) (Figure 4A) while ABA to control allergen remained stable; median went from 0.8 to 1.4 ($P = 1.0$) (Figure 4B). Two TS became 'non-responders' in CD-sens at the end of the study; hence, ABA could not be calculated. Since omalizumab suppresses CD-sens, final visit ABA was not calculated for TF.

Significant correlations were seen between ABA and IgG4-ab; peanut ($\rho = .67$ $P = .0499$), Ara h 2 ($\rho = .70$ $P = .036$), Ara h 6 ($\rho = .70$ $P = .036$), IgG-ab and ABA showed somewhat lower correlations that were not significant ($\rho = .6-.65$ $P = .58-.088$).

4 | DISCUSSION

In this study, peanut allergic adolescents with a history of severe allergic reactions to peanut started pOIT after an individualized omalizumab pre-treatment. After pOIT maintenance dose was reached, omalizumab was lowered guided by CD-sens and medical history.

TABLE 2 Adverse events during pOIT treatment

Total peanut doses	Total (n = 17)			Treatment success (TS), (n = 11)			Treatment failure (TF), (n = 6)		
	12 915			6978			5937		
Peanut doses per child, mean (range)	760 (336-1163)			634 (336-1093)			990 (804-1163)		
	Patients with event ^a , n (%)	Mean number of events per patient with event ^a (range)	Doses with dosing event ^a , n (%)	Patients with event ^a , n (%)	Mean number of events per patient with event ^a (range)	Doses with dosing event ^a , n (%)	Patients with event ^a , n (%)	Mean number of events per patient with event ^a (range)	Doses with dosing event ^a , n (%)
Symptoms									
Skin									
Urticaria	7 (41.2)	1.9 (1-3)	13 (0.1)	3 (27.3)	1.3 (1-2)	4 (0.1)	4 (66.7)	2.3 (1-3)	9 (0.2)
Erythema-flush	1 (5.9)	6.0 (6)	6 (0.0)	0	-	0 (0)	1 (16.7)	6.0 (6)	6 (0.1)
Angioedema	2 (11.8)	2.0 (1-3)	4 (0.0)	1 (9.1)	1.0 (1)	1 (0.0)	1 (16.7)	3.0 (3)	3 (0.1)
Pruritus	9 (52.9)	2.8 (1-8)	25 (0.2)	4 (36.4)	2.0 (1-3)	8 (0.1)	5 (83.3)	3.4 (1-8)	17 (0.3)
Gastrointestinal									
Vomiting	2 (11.8)	1.5 (1-2)	3 (0.0)	1 (9.1)	1.0 (1)	1 (0.0)	1 (16.7)	2.0 (2)	2 (0.0)
Severe abdominal pain	5 (29.4)	1.2 (1-2)	6 (0.0)	3 (27.3)	1.3 (1-2)	4 (0.1)	2 (33.3)	1.0 (1)	2 (0.0)
Respiratory									
Conjunctivitis	2 (11.8)	1.0 (1)	2 (0.0)	1 (9.1)	1.0 (1)	1 (0.0)	1 (16.7)	1.0 (1)	1 (0.0)
Rhinitis	4 (23.5)	6.3 (1-21)	25 (0.2)	1 (9.1)	1.0 (1)	1 (0.0)	3 (50.0)	8.0 (1-21)	24 (0.4)
Cough	1 (5.9)	1.0 (1)	1 (0.0)	0	-	-	1 (16.7)	1.0 (1)	1 (0.0)
Subj. throat tightness	8 (47.1)	1.8 (1-4)	14 (0.1)	3 (27.3)	1.3 (1-2)	4 (0.1)	5 (83.3)	2.0 (1-4)	10 (0.2)
Chest tightness	2 (11.8)	1 (1)	2 (0.0)	0	-	0 (0*)	2 (33.3)	1.0 (1)	2 (0.0*)
Subj. breathing diffic.	9 (52.9)	2.8 (1-8)	25 (0.2)	4 (36.4)	1.4 (1-4)	8 (0.1)	5 (83.3)	3.4 (1-8)	17 (0.3)
Wheeze	0 (0)	-	0 (0)	0	-	0 (0)	0	-	0 (0)
Hypoxaemia (sat < 92%)	1 (5.9)	1.0 (1)	1 (0.0)	1 (9.1)	1.0 (1)	1 (0.0)	0	-	0 (0)
Neurolog.-cardiovascular									
Chest pain	2 (11.8)	2.0 (2)	4 (0.0)	1 (9.1)	2.0 (2)	2 (0.0)	1 (16.7)	2.0 (2)	2 (0.0)
Dizziness	2 (11.8)	1.0 (1)	2 (0.0)	1 (9.1)	1.0 (1)	1 (0.0)	1 (16.7)	1.0 (1)	1 (0.0)
Syncope	1 (5.9)	1.0 (1)	1 (0.0)	1 (9.1)	1.0 (1)	1 (0.0)	0	-	0 (0)
Hypotension	0	-	0 (0)	0	-	0 (0)	0	-	0 (0)
Systemic REACTIONS^a									
	12 (70.6)	3.1 (1-14)	37 (0.3)	6 (54.6)	1.7 (1-3)	10 (0.1)	6 (100)	4.5 (1-14)	27 (0.5)
Mild ^c	8 (47.1)	2.1 (1-7)	19 (0.1)	5 (45.5)	1.2 (1-2)	6 (0.1)	3 (50)	4.3 (2-7)	13 (0.2)
Moderate ^d	7 (41.2)	2.4 (1-7)	17 (0.1)	2 (18.2*)	1.5 (1-2)	3 (0.0*)	5 (83.3*)	2.8 (1-7)	14 (0.2*)
Severe ^e	1 (5.9)	1 (1)	1 (0.0)	1 (9.1)	1 (1)	1 (0.0)	0	-	0 (0)

(Continues)

TABLE 2 (Continued)

Total (n = 17)			Treatment success (TS), (n = 11)			Treatment failure (TF), (n = 6)			
12 915			6978			5937			
760 (336-1163)			634 (336-1093)			990 (804-1163)			
Peanut doses per child, mean (range)	Patients with event ^a , n (%)	Mean number of events per patient with event ^a (range)	Doses with dosing event ^a , n (%)	Patients with event ^b , n (%)	Mean number of events per patient with event ^b , (range)	Doses with dosing event ^b , n (%)	Patients with event ^b , n (%)	Mean number of events per patient with event ^b , (range)	Doses with dosing event ^b , n (%)
Therapy administered									
Use of Im adrenaline	8 (47.1)	1.9 (1-4)	15 (0.1)	3 (27.3)	1.7 (1-3)	5 (0.1*)	5 (83.3)	2 (1-4)	10 (0.2*)
At home	7 (41.2)	1.9 (1-3)	13 (0.1)	2 (18.2*)	2 (1-3)	4 (0.1*)	5 (83.3*)	1.8 (1-3)	9 (0.2*)
In ambulance/hospital	2 (11.8)	1 (1)	2 (0.0)	1 (9.1)	1 (1)	1 (0.0)	1 (16.7)	1 (1)	1 (0.0)
Repeated doses	1 (5.9)	1 (1)	1 (0.0)	0	-	-	1 (16.7)	1 (1)	1 (0.0)
Use of inhaled b-2 agonist	7 (41.2)	1.7 (1-3)	12 (0.1)	3 (27.3)	1.7 (1-3)	5 (0.1)	4 (66.7)	1.8 (1-2)	7 (0.1)
At home	7 (41.2)	1.7 (1-3)	12 (0.1)	3 (27.3)	1.7 (1-3)	5 (0.1)	4 (66.7)	1.8 (1-2)	7 (0.1)
In ambulance/hospital	1 (5.9)	1 (1)	1 (0.0)	1 (9.1)	1 (1)	1 (0.0)	0	-	0 (0)
Intravenous fluid	2 (11.8)	1 (1)	2 (0.0)	2 (18.2)	1 (1)	2 (0.0)	0	-	0 (0)
ED-visit	7 (41.2)	1.9 (1-3)	13 (0.1)	3 (27.3)	1.7 (1-2)	5 (0.1)	4 (66.7)	2.0 (1-3)	8 (0.1)
Hospital admission	2 (11.8)	1 (1)	2 (0.0)	0	-	0 (0*)	2 (33.3)	1 (1)	2 (0.0*)

Note: Peanut doses, allergic symptoms, administered medical therapy and ED-visits in relation to outcome.

Abbreviations: diffic., difficulties; im, intramuscular; Subj., subjective.

^aSystemic reaction = dose-related allergic reaction with involvement of ≥2 organ systems.

^bEvent = peanut dose-related symptom, systemic reaction, administered therapy or ED-visit.

^cMild systemic reaction = systemic reaction but not anaphylaxis.

^dModerate systemic reaction = anaphylaxis grade 1-2.

^eSevere systemic reaction = anaphylaxis grade 3.

*TF vs TS: P-value < .05.

TABLE 3 IgG-antibodies (IgG-ab) and IgG4-antibodies (IgG4-ab)

IgG-ab and IgG4-ab mg/L, median (25th-75th percentile)	Total n = 17	Treatment success (TS) n = 11	Treatment failure (TF) n = 6	P
Baseline				
Peanut IgG	9.5 (5.5-13.5)	8.5(4.9-11.4)	12.7 (9.5-16.4)	.16
Ara h 2 IgG	6.7 (4.5-13.4)	6.7 (3.5-14.5)	7.8 (4.9-13.4)	.61
Ara h 6 IgG	2.8 (2-3.5)	2 (<2-3.5)	3.4 (2.8-4.8)	.01
Peanut IgG4	0.39 (0.23-0.56)	0.38 (0.13-0.56)	0.42 (0.29-0.67)	.61
Ara h 2 IgG4	0.20 (0.10-0.28)	0.11 (0.07-0.20)	0.28 (0.28-0.42)	.004
Ara h 6 IgG4	0.063 (0.024-0.20)	0.045 (0.01-0.063)	0.22 (0.081-0.42)	.007
Start OIT				
Peanut IgG	10.0 (5.6-12.4)	8.7 (5.0-10.6)	12.1 (10.7-13.8)	.06
Ara h 2 IgG	7.3 (3.8-15.8)	7.3 (3.7-15.8)	7.4 (5.2-17.0)	.61
Ara h 6 IgG	2.8 (2.3-3.6)	2.4 (2-3.6)	2.9 (2.8-4.3)	.11
Peanut IgG4	0.38 (0.20-0.56)	0.37 (0.13-0.61)	0.40 (0.32-0.56)	.42
Ara h 2 IgG4	0.16 (0.08-0.24)	0.10 (0.05-0.17)	0.26 (0.21-0.37)	.005
Ara h 6 IgG4	0.052 (0.024-0.13)	0.028 (0.01-0.062)	0.19 (0.12-0.33)	.006
Maintenance phase				
Peanut IgG	44.6 (31.7-58.1)	52.5 (31.7-66.7)	43.8 (35.2-45.6)	.55
Ara h 2 IgG	27.6 (18.8-35.0)	31.9 (19.3-39.1)	21.6 (15.9-27.6)	.19
Ara h 6 IgG	18.6 (14.2-22.2)	20.8 (13.3-27.2)	16.7 (14.2-21.5)	.32
Peanut IgG4	5.82 (4.31-9.57)	5.7 (2.6-12.8)	8.2 (4.6-9.6)	.42
Ara h 2 IgG4	4.31 (2.83-7.87)	3.63 (1.90-8.25)	4.90 (2.83-7.54)	.69
Ara h 6 IgG4	4.11 (1.88-9.06)	4.11 (1.58-9.71)	5.50 (3.93-9.06)	.84
End of study				
Peanut IgG	28.7 (17.6-64.4)	47.6 (21.4-128)	23.2 (16.9-41.7)	.27
Ara h 2 IgG	29.2 (13.7-57.3)	42.6 (13.7-59.4)	19.8 (16.4-27.9)	.07
Ara h 6 IgG	13.6 (7.09-45.7)	38.9 (8.09-75.4)	10.1 (6-13.6)	.11
Peanut IgG4	14.5 (4.49-55)	26.0 (3.62-74)	10.1 (4.49-19.8)	.42
Ara h 2 IgG4	10.5 (2.88-45)	29.2 (4.76-52)	8.36 (2.19-12.6)	.16
Ara h 6 IgG4	11.2 (3.73-48)	34 (4.18-67)	6.8 (0.92-11.2)	.07

Note: IgG-ab and IgG4-ab to peanut and peanut components Ara h 2 and Ara h 6 measured at baseline, start of pOIT, 8 wk into maintenance phase and at the final visit. Treatment successes (TS) vs. treatment failures (TF) (Mann-Whitney U test). *P*-values <.05 in bold.

The primary outcome, tolerating pOIT for 12 weeks after stopping omalizumab, assessed by medical history and passing an open challenge to the maintenance pOIT dose was met by 48% (TS group). During treatment, TS had significantly fewer systemic reactions and adrenaline injections than the treatment failure group (TF). TS also differed to TF concerning immunological markers with significantly lower IgE-ab to peanut and Ara h 2, lower CD-sens at baseline and a more pronounced IgG4-ab increase during the study. At the final visit, where omalizumab had been stopped for 12 weeks (TS) or omalizumab doses had been decreased (TF), in vitro basophil allergen threshold sensitivity (CD-sens) and basophil reactivity to peanut started to increase. This increase was more pronounced among TF, despite the fact that they were still treated with omalizumab at doses capable of suppressing CD-sens values to the control allergen.

Systemic reactions, especially in the TF group, occurred to a vast extent (81%) during the final stages of the study as omalizumab had been decreased by ≥75% of the patient's dose at the initiation of pOIT, coinciding with the increased basophil sensitivity/reactivity.

The positive effects of omalizumab in this study were most notable during up-dosing of pOIT, as high starting pOIT doses and rapid up-dosing were well tolerated. The starting dose of 280 mg peanut protein is, as far as we know, the highest reported for pOIT with or without omalizumab.^{17,18,35,36} All our subjects reached the 2800 mg maintenance dose, TS significantly faster. Two other studies have assessed the ability to reach a 2000 mg dose at week 20, which was achieved in 78% and 92%, respectively.^{18,35} This was not a primary outcome in our study although post hoc analysis generated a 96% success rate of reaching 2800 mg by week 20.

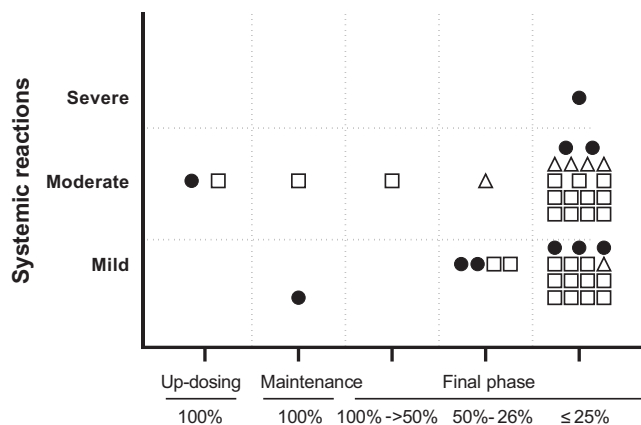


FIGURE 2 Systemic allergic reactions in relation to phase of study and omalizumab dose (where 100% omalizumab is the dose given at initiation of pOIT). ● Treatment success, □ Treatment failure, Δ Drop-out

AEs are common in OIT and severe reactions are most common during up-dosing.³⁷ Omalizumab has been shown to facilitate OIT and to reduce AEs.^{18,24,35} In our study, systemic reactions occurred in 0.3% and adrenaline was administered after 0.1% of pOIT doses, mainly during maintenance phase as omalizumab doses were reduced, which is in-line with previous studies.^{18,35} Worth noting is that one patient alone experienced 14 systemic reactions (of the 43 systemic reactions in the whole study population). TF received adrenaline more often (5/6 patients or 83%) than TS (3/11 patients or 27%) most commonly after skin symptoms and subjective breathing difficulties. Beside the single severe systemic allergic reaction, no objective signs of respiratory distress were observed by healthcare providers. Although the frequency of significant reactions per peanut dose was low in our study, the risk for each subject was substantial given that doses were given daily over a long period. Our design allowed for rapid and safe up-dosing but seems to postpone the problem of adverse events and one can ask which is better.

It is difficult to compare success rates and AEs between studies (with or without omalizumab) as for example age, allergy severity, outcomes and AE-scoring systems differ. Our adolescent study population is similar to the paediatric study population in a pOIT study without omalizumab, by Blumchen et al (patients with peanut induced anaphylaxis).³⁶ They reported objective symptoms with a frequency of 2.6% (1.3% respiratory, which is substantially higher than our frequency of respiratory symptoms of 0.2%). Additionally, our subjects received higher pOIT doses which provide support for the protective effects of omalizumab that have been proposed in other trials and recently published reviews/guidelines.^{5,18,20,37}

The 26% drop-out rate was quite high in our study, but this can at least partially be explained by the long treatment duration. Other pOIT studies report early dropouts; however, our patients dropped out at a median of 72 weeks into pOIT (first drop-out after 8.5 months). Besides, most pOIT studies have reported results from

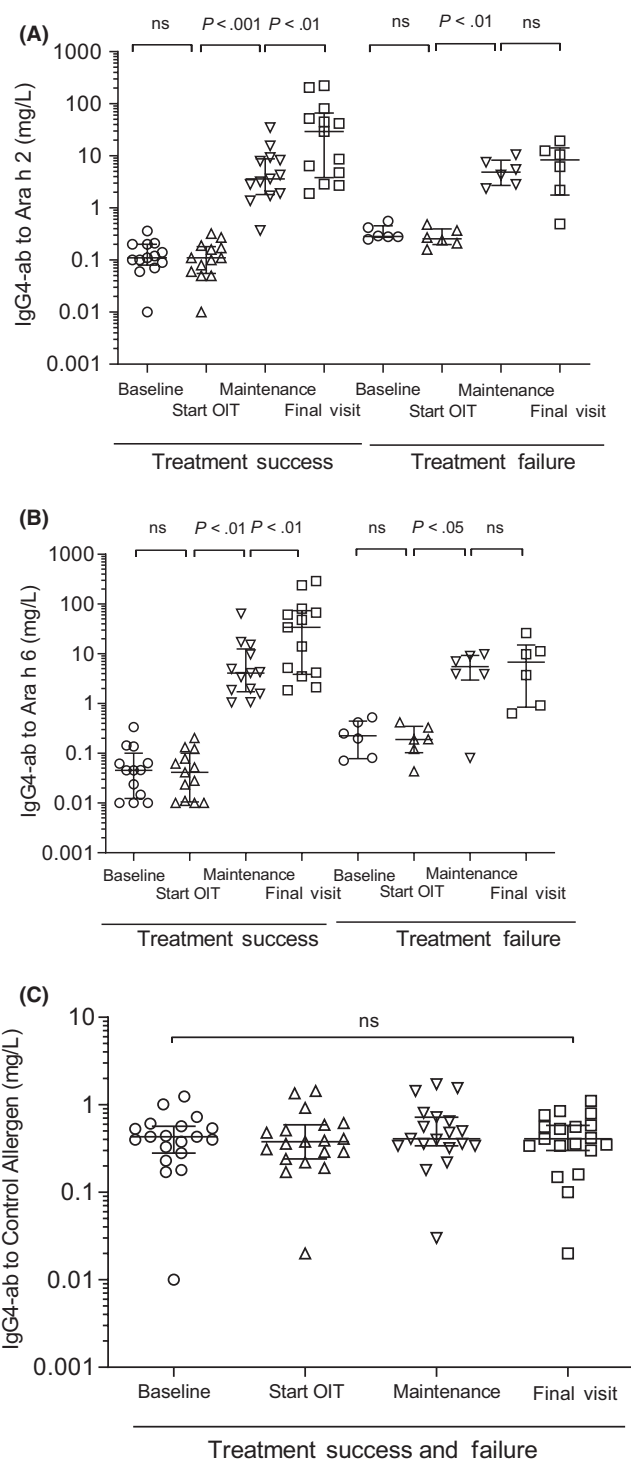


FIGURE 3 IgG4-ab levels at: ○ Baseline, Δ Start of OIT, ▽ Maintenance Phase, □ Final Visit. A, Ara h 2, B, Ara h 6, C, Control allergen. Error bars are presented as median (inter quartile range). A statistical significance was considered at a P-value of <.05

≤1 year of pOIT^{14,17,18,35,36,38} possibly leading to an over-estimation of positive effects. We observed that most of our adolescent patients had periods when motivation was lacking. We speculate that adolescence might not be the optimal time for initiation of OIT. It seems like younger patients respond better to treatment.¹⁷ Vickery

TABLE 4 CD-sens, basophil reactivity, basophil count, IgE on basophils, FcεRI on basophils

	Total	Treatment success (TS)	Treatment Failure (TF)	P
CD-sens to peanut				
Baseline, whole blood	0.8 (0.4-1.9)	0.5 (0.3-1.5)	6.7 (1.5-9.5)	.02
Baseline, washed	1.9 (1.5-10)	1.7 (1.3-6.9)	8.2 (1.8-35)	.1
Start OIT, whole blood	0	0	0	.65
Start OIT, washed	0.2 (0.2-0.5)	0.2 (0-0.5)	0.3 (0.2-0.5)	.24
Maintenance phase, whole blood	0	0	0	.51
Maintenance phase, washed	0.2 (0-0.4)	0.2 (0.1-0.4)	0.1 (0-0.5)	.58
Final visit, whole blood	0.1 (0-0.5)	0 (0-0.3)	0.4 (0.1-0.6)	.06
Final visit, washed	2.1 (0.9-3.5)	1.8 (0.9-2.4)	3 (1.1-3.8)	.3
CD-sens to control allergen				
Baseline, whole blood	4.2 (2.3-7.8)	3.8 (2.2-31)	5.6 (2.9-7.3)	1.0
Baseline, washed	3.4 (0.1-8.6)	2.8 (0.1-8.6)	7.6 (3.1-11.9)	.18
Final visit, whole blood	0.9 (0.3-2.6)	2.5 (0.9-4.5)	0.3 (0.1-0.4)	.007
Final visit, washed	0.2 (0-2.9)	2.2 (0-8.6)	0 (0-0.3)	.13
Basophil reactivity to peanut				
Baseline, whole blood	54.1 (43.9-67.5)	54.1 (29.3-59.4)	58.4 (43.9-68.6)	.62
Baseline, washed	38.7 (22.5-56.1)	37.1 (21.4-52.0)	47.5 (30.3-62.0)	.31
Start OIT, whole blood	6.9 (5.5-15.5)	6.5 (5.2-13.0)	11.2 (6.1-15.8)	.37
Start OIT, washed	21.2 (13.1-29.5)	19.3 (11.5-25.2)	30.6 (21.2-32.4)	.09
Maintenance phase, whole blood	1.4 (0.7-1.9)	1.3 (0.7-1.4)	2.1 (1.0-11.6)	0.13
Maintenance phase, washed	21.2 (14.9-33.2)	21.2 (15.4-32.0)	23.2 (12.1-51.0)	.92
Final visit, whole blood	30.3 (8.8-55.4)	17.6 (5.1-31.5)	49.2 (32.5-56.7)	.03
Final visit, washed	45.2 (30.0-56.9)	51.5 (13.2-58.9)	45.1 (30.0-49.4)	.92
Basophil reactivity to control allergen				
Baseline, whole blood	38.0 (28.8-58.7)	29.5 (24.3-58.7)	47.3 (38.0-65.6)	.11
Baseline, washed	22.3 (11.2-38.4)	15.1 (6.9-41.2)	30.4 (22.3-38.4)	.19
Final visit, whole blood	24.4 (14.0-54.4)	20.9 (11.3-64.9)	32.0 (19.8-45.9)	1.0
Final visit, washed	13.2 (8.5-31.6)	13.2 (6.8-57.0)	13.6 (8.5-22.5)	.84
Basophil count				
Baseline	26 (18-47)	26 (18-47)	27 (18-48)	.92
Start OIT	25 (19-31)	25 (23-31)	25 (16-51)	.96
Maintenance phase	39 (26-55)	37 (26-72)	44 (21-55)	.88
Final visit	33 (26-39)	30 (23-38)	39 (29-44)	.21
IgE on basophils/ μL blood $\times 10^3$				
Baseline	1067 (610-1424)	1067 (599-1250)	1020 (610-1844)	1.0
Start OIT	24 (17-37)	24 (17-33)	30 (6-47)	.92
Maintenance phase	34 (19-65)	39 (20-79)	18 (10-24)	.03
Final visit	372 (273-1110)	849 (293-1150)	216 (49-331)	.02
FcεRI on basophils/ μL blood $\times 10^3$				
Baseline	701 (410-978)	701 (410-924)	724 (355-1114)	1.0
Start OIT	57 (46-82)	62 (49-106)	48 (32-76)	.27
Maintenance phase	81 (64-147)	116 (74-166)	67 (44-81)	.11
Final visit	324 (137-536)	378 (163-772)	176 (51-324)	.06

Note: CD-sens to peanut and control allergen untreated and washed samples. Basophils/ μL blood. IgE on basophils = Total number of IgE-ab on basophil cell surface. FcεRI on basophils/ μL blood $\times 10^3$ = Total number of FcεRI on basophil cell surface. Reported as median (25th-75th percentile). Treatment successes (TS) vs. treatment failures (TF) (Mann-Whitney U test). P-values <.05 in bold.

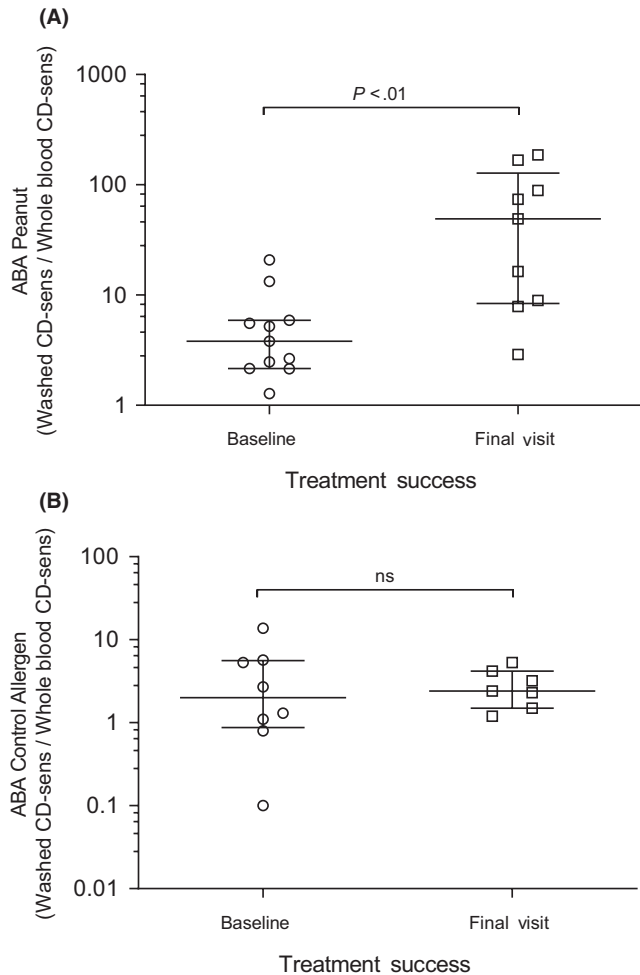


FIGURE 4 ABA in the TS group at baseline and final visit. A, Peanut and B, Control allergen. Two TS patients became 'non-responders' in CD-sens at the end of the study; hence ABA could not be calculated. ABA cannot be calculated in TF since they were still on treatment with omalizumab. Error bars are presented as median (inter quartile range). A statistical significance was considered at a P -value of $< .05$

et al reported impressive results in toddlers; 78% of patients tolerated 5 g peanut protein 4 weeks after stopping OIT that had been ongoing for, in median, 29 months. Despite the long treatment in this study, only 14% dropped out and significant AEs were rare.³⁹ Therefore, we believe that starting pOIT early is beneficial. The fact that 12/23 patients either dropped out or failed to complete our study might also be due to the high maintenance dose that was reached rapidly, a maintenance dose that was no longer tolerated for some patients as omalizumab doses were tapered.

Successful OIT has been associated with low peanut and milk IgE-ab pre-treatment, while high baseline IgE-ab to, for example peanut, Ara h 2, milk and casein, high ratio of IgE-ab/total IgE and large SPT weal were associated with OIT failure.^{19,20,36,40,41} We found that TS had lower baseline IgE-ab to peanut and Ara h 1, 2 and 3. One could speculate if treatment failure is a result of a more severe allergy or an effect of high peanut and peanut component IgE-titres, possibly by lowering the IgG4/IgE-ab-ratio.

Increasing IgG and IgG4-levels are seen both in spontaneous resolution of allergy and successful allergen immunotherapy.^{19,42-44} In our study, IgG and IgG4 showed diverging patterns; IgG4-ab continued to increase throughout maintenance therapy whereas IgG-ab plateaued/decreased. Similar observations were made in another long-term pOIT study.¹⁹ However, contradictory to that study, we observed that TS had a more pronounced continued increase in IgG4-ab (peanut, Ara h 2 and Ara h 6) than TF during maintenance phase and based on our data it is tempting to suggest that the ability to continuously amplify IgG4-ab-titres is a key feature for successful pOIT. Still, treatment failures also increased their IgG/IgG4-levels but to a lesser extent. These patients could also lower their omalizumab doses, but at a slower pace and they were not able to completely stop omalizumab treatment.

The postulated mechanism that allergen IgG4-ab may block allergen-IgE-ab interactions⁴⁵ seems to play a role in our study. POIT resulted in significantly decreased basophil allergen sensitivity to peanut in whole blood but not in washed blood resulting in an increased ABA, and we observed clear correlations between IgG4-ab and ABA. Taking into account the data from the control allergens, it appears that these changes were induced by pOIT and not by omalizumab. For the control allergen, neither IgG-ab/IgG4-ab nor ABA increased during the study. Neither did CD-sens differ significantly between baseline and final visit to the control allergens. Median CD-sens to control allergen at final visit was 72% (36%-113%) of the baseline value among TS, whereas the median CD-sens to peanut was 3% (2%-30%) of the baseline values.

CD-sens increases as the omalizumab dose is tapered which is logical, even though we had expected that the OIT would have induced enough blocking agents to compensate for the gradually decreasing effects of omalizumab, resulting in lower CD-sens and better clinical outcomes in a larger proportion of study subjects.

Our data, as well as previous publications^{42,46} imply that desensitization of mast cells and basophils is not dependent on decreasing IgE-ab. However, decreased IgE via omalizumab treatment prior to OIT allows for much higher antigen doses in the escalation phase.^{18,20,23} We found a $> 90\%$ reduction of IgE and FcεRI on basophils after omalizumab treatment that after cessation of omalizumab started to approach baseline levels.

Weaknesses of the present study include the small study population and lack of placebo arm; hence, all results should be considered as exploratory and need to be further studied. The main rationale for not having a placebo arm was patient safety, and the study protocol starting at 280 mg peanut protein would not have been appropriate for a placebo-controlled study. Instead of a control or placebo group, all study patients had a concomitant airborne allergy to pollen/pets for which the patient did not receive immunotherapy, and we could observe clear discrepancies in treatment-induced immunological changes between the treated allergy (peanut) and the control allergen. When planning this study, we believed that a rapidly reached and high maintenance dose would be advantageous as this would lead to a long period with high allergen exposure. But for some patients, especially in

the TF group this could actually have been a disadvantage; recent data from Vickery et al also suggest that a high maintenance dose is not necessarily better.³⁹ Another limitation is that we used patient- and parent-reported symptoms of AE to assess the severity of allergic reactions as most reactions occurred at home and not in the clinic. Finally, our highly individualized study protocol, where both clinical symptoms and CD-sens were used to guide omalizumab de-escalation, hampers generalizability. Despite the lack of a placebo arm, we believe that this study corroborates previous findings that omalizumab facilitates initiation of pOIT by reducing AEs and allowing more rapid up-dosing,^{18,35} but whether it affects long-term outcomes remains elusive.

The main strength of our study is the homogeneous study population of highly sensitized peanut allergic patients with a history of anaphylactic reactions, the category that likely will benefit most from successful treatment. OIT is likely to become more available in clinical, non-research settings after the publication of the EAACI immunotherapy guidelines.⁵ Hence true, phenotype-specific prognostic figures are imperative for patients facing the decision of starting a long and often troublesome treatment, something that studies with heterogeneous study populations cannot provide with sufficient accuracy. Besides, the treatment period in this study is long, providing more realistic long-term outcome measures. We continue to monitor the patients still treated with pOIT during an additional 3-years of pOIT without omalizumab. The preliminary long-term data suggest that allergic reactions become less frequent and that the reactions that do occur seem to occur during times of worse compliance. Long-term compliance seems to be a major concern for pOIT even among patients not experiencing allergic reactions, mainly due to a taste aversion to peanuts.

We conclude that omalizumab with CD-sens guided individualized dosing allows for a safe initiation and rapid up-dosing of peanut OIT but it does not seem like this approach will lead to improved long-term effects from pOIT.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

ORCID

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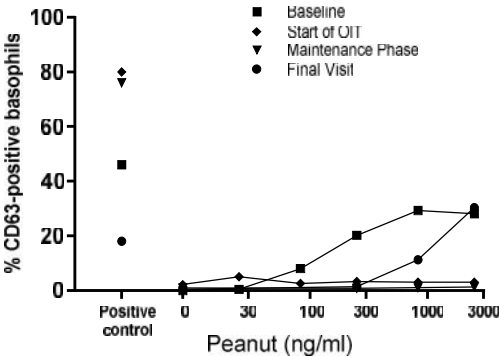
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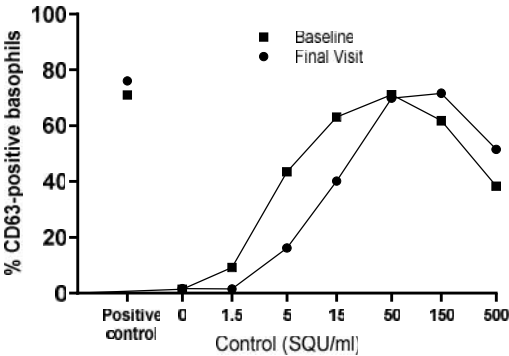
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E-figure 1

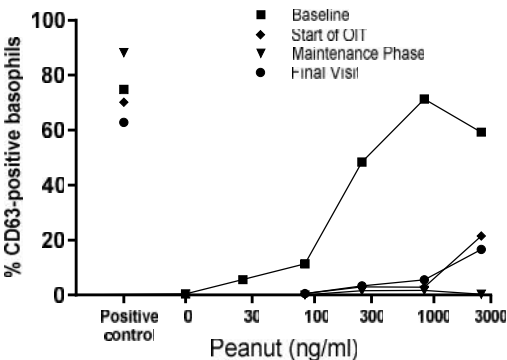
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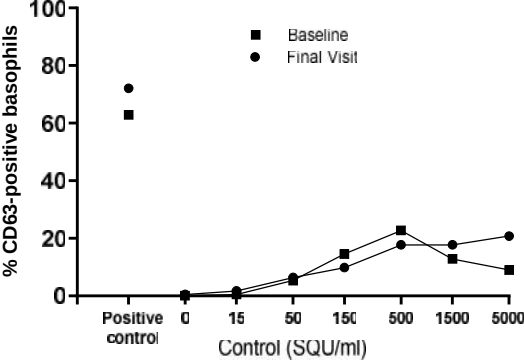
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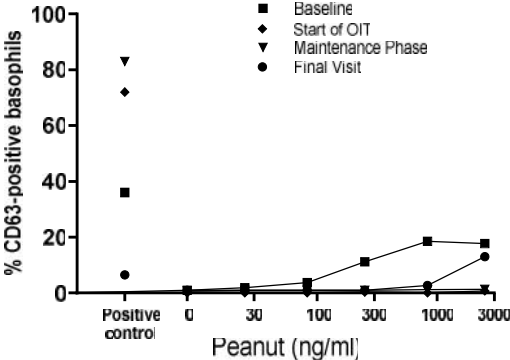
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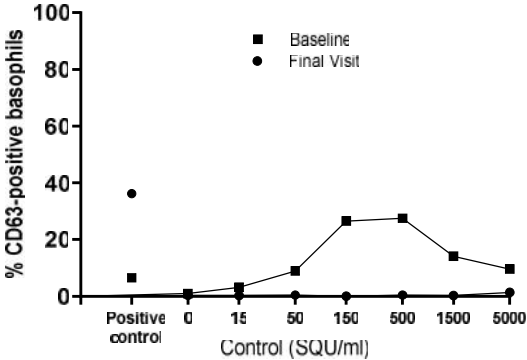
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E-table 1. Adverse events for all patients

	Treatment successes (TS) (n= 11)			Treatment failures(TF) (n= 6)			Drop-outs (n = 6)		
Total peanut doses	6978			5937			3180		
Peanut doses per child, mean (range)	634 (336-1093)			990 (804-1163)			530 (294-781)		
	Patients with event ^b n(%)	Mean number of events per patient with event ^b (range)	Doses with dosing event ^b n(%)	Patients with event ^b n(%)	Mean number of events per patient with event ^b (range)	Doses with dosing event ^b n(%)	Patients with event ^b n(%)	Mean number of events per patient with event ^b (range)	Doses with dosing event ^b n(%)
SYMPTOMS									
Mild oropharyngeal	9(81.8)	N/a	N/a	6(100)	N/a	N/a	6(100)	N/a	N/a
Skin									
Urticaria	3(27.3)	1.3(1-2)	4(0.1)	4(66.7)	2.3(1-3)	9(0.2)	3(50)	1.3(1-2)	4(0.1)
Erythema-flush	0	-	0(0)	1(16.7)	6.0(6)	6(0.1)	0	-	0(0)
Angioedema	1(9.1)	1.0(1)	1(0.0)	1(16.7)	3.0(3)	3(0.1)	0	-	0(0)
Pruritus	4(36.4)	2.0(1-3)	8(0.1)	5(83.3)	3.4(1-8)	17(0.3)	1(16.7)	2.0(2)	2(0.1)
Gastrointestinal									
Emesis	6(54.6)	N/a	N/a	4(66.7)	N/a	N/a	4(66.7)	N/a	N/a
Mild abdominal pain	3(27.3)	N/a	N/a	5(83.3)	N/a	N/a	4(66.7)	N/a	N/a
Emesis or mild abd pain	7(63.6)	N/a	N/a	5(83.3)	N/a	N/a	6(100)	N/a	N/a
Vomiting	1(9.1)	1.0(1)	1(0.0)	1(16.7)	2.0(2)	2(0.0)	0	-	0(0)
Severe abdominal pain	3(27.3)	1.3(1-2)	4(0.1)	2(33.3)	1.0(1)	2(0.0)	1(16.7)	2.0(2)	2(0.1)
Respiratory									
Conjunctivitis	1(9.1)	1.0(1)	1(0.0)	1(16.7)	1.0(1)	1(0.0)	2(33.3)	1.5(1-2)	3(0.1)
Rhinitis	1(9.1)	1.0(1)	1(0.0)	3(50.0)	8.0(1-21)	24(0.4)	1(16.7)	1.0(1)	1(0.0)
Cough	0	-	0(0)	1(16.7)	1.0(1)	1(0.0)	0	-	0(0)
Subj. throat tightness	3(27.3)	1.3(1-2)	4(0.1)	5(83.3†)	2.0(1-4)	10(0.2†)	0†	-	0(0†)
Chest tightness	0	-	0(0*)	2(33.3)	1.0(1)	2(0.0*)	0	-	0(0)
Subj. breathing difficult	4(36.4)	1.4(1-4)	8(0.1)	5(83.3)	3.4(1-8)	17(0.3)	4(66.7)	1.3(1-2)	5(0.2)
Wheeze	0	-	0(0)	0	-	0(0)	0	-	0(0)
Hypoxemia (sat<92%)	1(9.1)	1.0(1)	1(0.0)	0	-	-	-	-	-
Neurolog.-cardiovascul.									
Chest pain	1(9.1)	2.0(2)	2(0.0)	1(16.7)	2.0(2)	2(0.0)	0	-	0(0)
Dizziness	1(9.1)	1.0(1)	1(0.0)	1(16.7)	1.0(1)	1(0.0)	0	-	0(0)
Syncope	1(9.1)	1.0(1)	1(0.0)	0	-	0(0)	0	-	0(0)
Hypotension	0	-	0(0)	0	-	0(0)	0	-	0(0)
Systemic reactions*	6(54.6)	1.7(1-3)	10(0.1)	6(100)	4.5(1-14)	27(0.5)	4(66.7)	1.5(1-2)	6(0.2)
In relation to OIT-phase									
Up-dosing	1(9.1)	1(1)	1(0.1)	1(16.7)	1(1)	1(0.2)	0	-	0(0)
Maintenance	6(54.6)	1.5(1-3)	9(0.1)	6(100)	4.3(1-14)	26(0.5)	4(66.7)	1.5(1-2)	6(0.2)
In relation to severity									
Mild ^c	5(45.5)	1.2(1-2)	6(0.1)	3(50)	4.3(2-7)	13(0.2)	1(16.7)	1(1)	1(0.0)
Moderate ^d	2(18.2*)	1.5(1-2)	3(0.0*†)	5(83.3*)	2.8(1-7)	14(0.2*)	4(66.7)	1.3(1-2)	5(0.2†)
Severe ^e	1(9.1)	1(1)	1(0.0)	0	-	0(0)	0	-	0(0)
THERAPY ADMINISTRED									
Use of i.m. adrenaline	3(27.3)	1.7(1-3)	5(0.1*)	5(83.3)	2(1-4)	10(0.2*)	2(33.3)	1.5(1-2)	3(0.1)
At home	2(18.2*)	2(1-3)	4(0.1*)	5(83.3*)	1.8(1-3)	9(0.2*)	2(33.3)	1(1)	2(0.1)
In ambulance/hospital	1(9.1)	1(1)	1(0.0)	1(16.7)	1(1)	1(0.0)	1(16.7)	1(1)	1(0.0)
Repeated doses	0	-	0(0)	1(16.7)	1(1)	1(0.0)	0	-	-
Inhaled b-2 agonist	3(27.3)	1.7(1-3)	5(0.1)	4(66.7)	1.8(1-2)	7(0.1)	2(33.3)	2(2)	4(0.1)
At home	3(27.3)	1.7(1-3)	5(0.1)	4(66.7)	1.8(1-2)	7(0.1)	2(33.3)	2(2)	4(0.1)
In ambulance/hospital	1(9.1)	1(1)	1(0.0)	0	-	0(0)	0	-	0(0)
Intravenous fluid	2(18.2)	1(1)	2(0.0)	0	-	0(0)	0	-	0(0)
ED-visit	3(27.3)	1.7(1-2)	5(0.1)	4(66.7)	2.0(1-3)	8(0.1)	1(16.7)	1(1)	1(0.0)
Hospital admission	0	-	0(0*)	2(33.3)	1(1)	2(0.0*)	0	-	0(0)

Peanut doses, symptoms, administered therapy and ED-visits among treatment successes (TS), treatment failures (TF) and drop-outs. *Systemic reaction = dose-related allergic reaction with involvement of ≥ 2 organ systems, ^bEvent = peanut dose related symptom, systemic reaction*,

administered therapy or ED-visit, ^cMild systemic reaction = systemic reaction but not anaphylaxis, ^d Moderate systemic reaction = anaphylaxis grade 1-2, ^e Severe systemic reaction = anaphylaxis grade 3, ^{*} TS vs TF: p-value <.05, [†] TS vs drop-outs: p-value < .05, [‡]TF vs drop-outs: p-value < .05.