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Coláiste na hOllscoile Corcaigh

Title

Probiotic peanut oral immunotherapy is associated with long-term persistence of 8-week sustained unresponsiveness and long-lasting quality-of-life improvement

Authors

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Key message

- There are few data on long-term effects and quality of life impact of peanut OIT.
- PPOIT was shown to induce 8-week sustained unresponsiveness that persists to 3-years post-treatment after *ad libitum* peanut ingestion.
- PPOIT provides lasting benefits for children with peanut allergy, with long-lasting improvement in health-related quality of life.

Conflicts of interest

Audrey Dunn Galvin reports having received consultant fees from DBV Technologies and Aimmune Therapeutics (Research grant; Advisory panel). Mimi LK Tang reports having received consultant fees from Pfizer, is an employee of, and holding share options/interest in, Prota Therapeutics and being an inventor on patents covering PPOIT. All other authors have no conflicts of interest to declare.

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Author contributions

PL and KCH drafted the manuscript. MLKT designed and supervised the study. KCH, SEA, ML, KSJ and ADG conducted the analysis. PL, KCH, ACL, SP, CJA, DT, ELS, MR ASYL participated in data collection, study conduct and administration. All authors provided feedback and critically reviewed the manuscript.

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Ethical Statement

This study was approved by the Royal Children's Hospital Human Research and Ethics Committee (reference number 35207). Prospective registration was with Australian New Zealand Clinical Trials Registry (ACTRN12615001275550). All participants provided informed consent.

Keywords

Peanut allergy, oral immunotherapy, probiotic, sustained unresponsiveness, health-related quality of life

To the Editor,

Peanut allergy persists for life in the majority of patients. Current management relies on allergen avoidance; however, ~50% of patients have accidental exposures within 1 year[2]. Peanut oral immunotherapy (OIT) is effective at inducing desensitization and can induce sustained unresponsiveness (SU) in a subset of treated patients, however data on long-term effectiveness and health-related quality of life (HRQL) impact are lacking. OIT-induced SU may be short-lived, with up to 67% of treatment responders losing their SU within 12-months[3]. Furthermore, a meta-analysis found that peanut OIT was associated with frequent adverse events (AE) and no significant improvement in HRQL[4].

We previously reported results from a proof-of-concept randomized trial (PPOIT-001), which showed that 18-months treatment with combined probiotic and peanut oral immunotherapy (PPOIT) induced 2-6 week SU in 74.2% of children aged 1-10 years[5]. Long-term follow-up of PPOIT-001 patients showed that PPOIT-induced SU persisted to 4-years post-treatment in 70% of

initial treatment responders[6]. Weaknesses of the PPOIT-001 study included participant selection based upon clinical history of reaction and positive peanut skin prick test (SPT) or specific-IgE (sIgE) rather than double-blind placebo-controlled food challenge (DBPCFC), and assessment of SU at 2-6 weeks post-treatment rather than after a longer period.

This open-label, single-arm study of PPOIT in children aged 1-12 years (PPOIT-002) addressed the above caveats by performing study entry DBPCFC (up to cumulative 4950mg peanut protein) to confirm peanut allergy and applying a more stringent SU assessment with a higher cumulative dose of peanut protein (4950mg) in the DBPCFC and longer 8-week period of peanut elimination prior to DBPCFC. Safety, HRQL and long-term outcomes were also evaluated. Eligibility criteria: age 1-12 years, >10kg in weight, failed DBPCFC to peanut and positive peanut SPT (≥3mm) or peanut sIgE (≥0.35 kUA/L). On Day 1 (T0), participants received increasing doses of peanut OIT (12% defatted peanut flour; Byrd Mill) every 20-minutes to a final dose of 12mg peanut protein (24mg cumulative). The daily dose of peanut OIT was increased every 2-weeks until a 2000mg maintenance dose was reached. This maintenance dose was continued until 18-months of PPOIT was completed. A single daily dose of probiotic (2×10^{10} cfu *Lactobacillus rhamnosus* GG ATCC 53103) was also administered. The primary endpoint was safety and tolerability. Secondary endpoints were: Desensitization at end-of-treatment (T2; DBPCFC, cumulative 4950mg peanut protein), SU at 8-weeks post-treatment (T3; DBPCFC, cumulative 4950mg peanut protein) and persistence of 8-week SU at 3-years post treatment in those subjects who achieved 8-week SU at T3 and were advised to ingest peanut *ad-libitum*[6] (T5; DBPCFC, cumulative 4950mg peanut protein). Persistent 8-week SU after 3 years of *ad libitum* intake at T5 was assessed by performing a DBPCFC (cumulative 4950 mg peanut protein) at the 3-year post-treatment timepoint, with strict secondary peanut elimination in the 8-weeks prior to challenge. Treatment-emergent AE (TEAE) during the treatment phase were graded according to National Institute of Health Consortium for Food Allergy Research criteria. TEAE are summarized by relationship to treatment and severity, presented according to medical dictionary for regulatory activities (MedDRA) terms and tabulated with descriptive statistics. Hypersensitivity refers to any reaction involving 2 or more organ systems. Immunological parameters (SPT; sIgE and sIgG4 against

peanut and peanut components Ara h1, h2, h3, h8, h9), parent proxy reported HRQL (validated Food Allergy Quality of Life Questionnaire-Parent Form, FAQLQ-PF) and parent's perception of adverse outcome for their child (Food Allergy Independent Measure, FAIM) were evaluated at T0, T2, T3 (SPT, sIgE, sIgG4), T4 (12-months post-treatment; FAQLQ-PF and FAIM) and T5.

Analyses of desensitization and SU were by intention-to-treat (ITT; all enrolled participants) and by complete case (participants with an end-of-treatment DBPCFC outcome) respectively. Persistence of SU at 3-years post-treatment was expressed as the proportion of participants with SU at T3 who maintained SU at T5. Between timepoint comparisons of parametric variables (SPT, HRQL) were by paired t-test and data presented as mean and standard deviation (SD). Non-parametric variables (sIgE, sIgG4) were analyzed using Wilcoxon rank-sum test and data presented as median and inter-quartile range (IQR), or standard t-test on logarithmic scaled values with data summarized as geometric mean and 95% confidence interval (95% CI). For HRQL outcomes, primary analysis used all available data at all timepoints. Statistical analyses were performed using Stata release 15 software (StataCorp, College Station, Tx) and R (R version 3.6.1). All participants provided informed consent. The Royal Children's Hospital Human Research and Ethics Committee provided ethical approval. Prospective registration was with Australian New Zealand Clinical Trials Registry (ACTRN12615001275550). Additional information about study methods and findings are available in the following repository: https://osf.io/d5uzn.

Twenty children were enrolled (mean age of 8.2 (SD, 3.0) years), four withdrew during treatment, 16 completed 18-months treatment and attended T2 and T3 DBPCFCs, 10 completed T5 DBPCFC (Figure 1). The reasons for withdrawal include lack of patient compliance (n=1), patient/caregivers decision to withdraw (n=2) and relocated while in the study (n=1). Table 1 presents participant baseline demographics. Seventy-five percent (15/20) and 60% (12/20) of participants achieved desensitization at end-of-treatment and 8-week SU at 8-weeks post-treatment, respectively (ITT); 94% (15/16) and 75% (12/16) by complete case, respectively. Of the 12 participants with SU at T3, 11 (91.7%) were evaluated for persistence of 8-week SU at

either 12-months post-treatment (n=5) or 3-years post-treatment (n=10). At T5, 6 (50%) of the 12 subjects who initially achieved SU at 8-weeks post-treatment still had persistent 8-week SU after 3 years of *ad libitum* intake at 3-years post-treatment. In the 3 years post-treatment, the median frequency of *ad libitum* peanut ingestion for those who had SU at 8-weeks post-treatment (T3) was between once a month or more and less than once a week (range less than once a month to 3-5 times a week), and median ingestion amount was 3-8 peanuts (range less than 1 peanut to 16 peanuts).

Peanut SPT wheal size decreased significantly from baseline to T2 (P=0.006) and reduction was sustained at both T3 (P=0.002) and T5 (P=0.001). Similar trends were seen for peanut sIgE (Table 1). Peanut sIgG4 increased significantly from baseline to T2 (p<0.001) with persistent increase at T3 (p=0.001) with similar findings for peanut component sIgG4 (Table 1). Corresponding reductions in peanut component Ara h1, h2, h3 sIgE levels and increases in Ara h1, h2, h3 sIgG4 levels were found at T2 and T3. At T5, participants with persistent SU (n=6) had lower peanut SPT wheal size (unadjusted P=0.06; age- and sex-adjusted P=0.05) and lower peanut sIgE level (unadjusted P=0.06; age- and sex- adjusted P=0.04) than subjects without persistent SU (n=4).

Seventeen participants (85%) reported 176 treatment-related AE, representing 8.8 AE per participant. The most frequent treatment-related AEs were abdominal pain, vomiting and hypersensitivity. The majority of treatment-related AEs were mild (93%, 164/176 events), with 8 (5%) moderate and 4 (2%) severe treatment-related AEs. There were no cases of eosinophilic esophagitis (EoE). Overall there were 12 moderate or severe treatment-related AE - 6 in the rush and buildup phases, of which 4 were anaphylaxis reactions and another 6 in the maintenance phase, of which all were anaphylaxis. Only 3 of the 10 anaphylaxis events were treated with epinephrine by participants/parents (2 in buildup phase, 1 in maintenance phase). No serious adverse events (SAEs) were reported. HRQL and parental perception of risk for their child (FAQLQ-PF and FAIM scores) both improved significantly from T2 to T5, with improvement greatly exceeding the 0.45 minimal clinically important difference (MCID) (Table 2). Significant

improvement was seen in both the food-related anxiety and social and dietary limitations subscales.

In summary, PPOIT induced desensitization in 75% (16/20) and 8-week SU in 60% (12/20) of patients, with SU persisting at 3-years post-treatment *ad libitum* peanut ingestion in 50% (6/12) of initial treatment responders. Importantly, this study applied a more robust measure of SU at end-of-treatment than in the PPOIT-001 trial, with DBPCFC performed after 8-weeks peanut elimination (rather than 2-6 weeks) and using a higher cumulative dose of peanut protein (4950mg vs. 4000mg). Findings confirm that lasting SU can indeed be achieved following PPOIT treatment, addressing caveats of the previous PPOIT-001 randomized trial. The low rate of natural resolution of peanut allergy during childhood supports the efficacy of PPOIT in the absence of a control group. The rate of SU in this study is similar to what has been reported for peanut OIT previously (30% - 78%)[3,11], and it is not possible to establish whether the addition of probiotic improved efficacy in the absence of a peanut OIT comparison group. The significant reduction in circulating peanut and peanut component sIgE levels, with persistent reduction out to 3-years post-treatment, suggests that PPOIT induced long-lasting redirection of the underlying allergic response. OIT causes frequent gastrointestinal symptoms that are associated with treatment discontinuation in 15%-20% of patients[13], and EoE has been reported in 2.7% to 5.3% of treated patients[14]. In this study, there were no treatment discontinuations due to gastrointestinal AEs despite a high 2000mg maintenance dose and no SAEs or EoE. Although the sample size is small, this could be explained by the addition of probiotic reducing OIT-induced gastrointestinal symptoms.

HRQL is vital to understand the patient experience and reflects treatment benefits that are not necessarily captured by other endpoints. Improvement in patient reported outcomes is also important when evaluating cost effectiveness and benefit over risk for a food allergy treatment, and the clinical meaningfulness of endpoint improvements, helping to redefine patient care. Importantly, PPOIT was associated with substantial HRQL improvement by 12-months post-

treatment that was sustained at 3-years post-treatment. Previous studies have reported improvement in HRQL during OIT compared with a parallel cohort control, with change in FAQLQ scores being comparable to those observed in our study[15], however, these previous studies only followed patients for 12-14 months. Our study tracked longitudinal changes in HRQL out to 4-years from commencing OIT (3-years post-treatment). It is important to note that HRQL was captured by parent-proxy report, and patient self-report may have revealed different findings.

This study has limitations, including the small sample size, single-arm open-label design and loss to follow-up of a small number of participants at later study time points. It is possible that patients with worsening HRQL due to treatment withdrawals were not captured. Despite these limitations, we observed favorable SU rates. Strengths of this study are the comprehensive assessments including clinical efficacy, immunological measures and HRQL, the long-term assessments at 3-years post-treatment, and the robust DBPCFC assessment of 8-week SU at end-of-treatment and 3-years post-treatment. Our findings confirm that lasting SU can indeed be achieved following PPOIT treatment, addressing caveats of the previous PPOIT-001 randomized trial. Importantly, persistence of SU was possible with *ad-libitum* intake of peanut in the years following treatment cessation. To conclude, PPOIT induced SU in a majority of treated patients, with persistence of SU to 3-years post-treatment after 3 years of *ad libitum* peanut ingestion and sustained HRQL improvements. Persistent SU was associated with lasting reduction in peanut sIgE, providing evidence that PPOIT modulated the underlying allergic response with durable effect. Further studies are needed to clarify whether the addition of probiotic to peanut OIT contributes to efficacy and/or safety.

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Table 1. Participant Demographics and Immunological Parameters

		PPOIT-002 study (n=20)
Age (y)	Median (IQR)	8.36 (6.34, 10.83)
	Mean (SD)	8.2 (3.0)
Male sex	n (%)	14 (70)
History of doctor-diagnosed eczema (ever), n (%)		8 (40)
History of doctor-diagnosed asthma (ever), n (%)		3 (15)
Reaction-eliciting dose (mg peanut protein) at study entry DBPCFC	Median	640
	Q1, Q3	320, 1016
Cumulative reaction-eliciting dose (mg peanut protein) at study entry DBPCFC	Median	1200
	Q1, Q3	560, 2572
Reaction-eliciting symptoms at study entry DBPCFC, n (%)		
	Upper respiratory tract	6 (30%)

	Cutaneous	9 (45%)
	Gastrointestinal	10 (50%)
	Lower respiratory tract	2 (10%)

Peanut SPT wheal size (mm)	Mean (SD), n	P-value*
Baseline	12.3 (4.5), 20	N/A
At end-of-treatment (T2)	7.0 (4.1), 16	0.006
At 8-weeks post-treatment (T3)	8.1 (4.4), 16	0.002
At 3-years post-treatment (T5)	7.3 (3.3), 13	0.001

Peanut sIgE (kUA/L)	Median (IQR), n	P-value**
Baseline	69.9 (7.9, 100.0), 20	N/A
At end-of-treatment (T2)	7.4 (1.2, 33.6), 15	<0.001
At 8-weeks post-treatment (T3)	10.2 (1.0, 27.6), 16	<0.001
At 3-years post-treatment (T5)	2.5 (1.0, 18.9), 12	0.002

Peanut sIgG4 (mgA/L)	Median (IQR), n	P-value**
Baseline	0.5 (0.2, 1.3), 16	N/A
At end-of-treatment (T2)	21.6 (6.0, 93.5), 15	<0.001
At 8-weeks post-treatment (T3)	11.2 (3.3, 28.4), 14	0.001

Peanut Ara h2 sIgE (kUA/L)		P-value**
Baseline	34.3 (3.4, 118.7), 16	N/A

At end of treatment (T2)	7.7 (0.9, 21.8), 15	<0.001
At 8-weeks post-treatment (T3)	10.9 (0.5, 18.4), 14	0.001

IQR = interquartile range, SD = standard deviation, SPT = skin prick test; *Paired t-test with equal variance; ** Wilcoxon signed rank test. P-values are derived from statistical comparisons between each timepoint with baseline.

Table 2. Difference in FAQLQ total scores between timepoints

Timepoints of interest	FAQLQ total score (points)*				FAIM total score (points)**			
	Sample size	Mean difference	P-value	95% CI	Sample size	Mean difference	P-value	95% CI
T0-T2	16	0.32	0.25	(-0.25, 0.90)	14	0.45	**0.05**	(-0.001, 0.91)
T0-T4	14	0.57	0.08	(-0.08, 1.22)	13	0.73	**0.003**	(0.30, 1.17)
T0-T5	10	0.65	0.08	(-0.08, 1.38)	12	0.79	**0.004**	(0.31, 1.27)
T2-T4	14	0.44	**0.004**	(0.17, 0.70)	13	0.37	**0.01**	(0.10, 0.65)

T2-T5	10	0.68	**0.04**	(0.04, 1.32)	12	0.47	**0.02**	(0.11, 0.84)
T4-T5	10	0.26	0.34	(-0.32, 0.84)	12	-0.08	0.83	(-0.93, 0.76)

*FAQLQ total score is a food allergy specific health-related quality of life measure (maximum of 30 questions; each scored 0-6; 0 representing best quality of life).

**FAIM total score assesses the parent's perception of the chance of an adverse outcome for the child with a food allergy (six questions with 6-point response scale; 0 (extremely unlikely) to 6 (extremely likely)).

Timepoints: T0 day 1, T2 end-of-treatment, T4 1-year post-treatment, T5 3-years post-treatment

Figure 1. CONSORT diagram of participant flow in the PPOIT-002 study

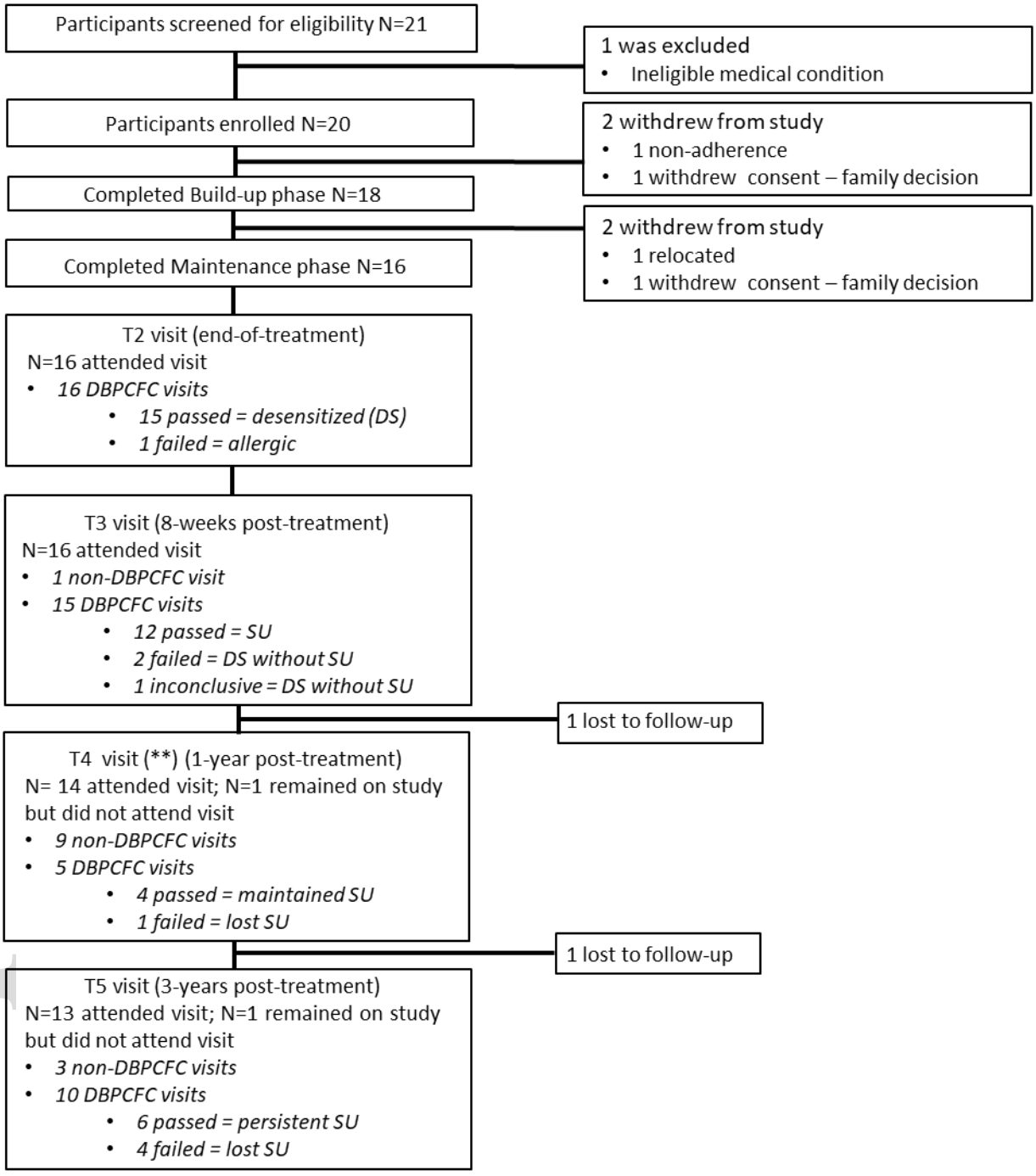

Figure footnotes: "Did not attend the visit" refers to subjects who did not attend the visit but remained contactable. "Lost to follow-up" refers to subjects who were not contactable at the follow-up visit. "Relocated" refers to subject moving overseas to another country. "Inconclusive" refers to subject who did not complete both parts of the DBPCFC. **T4 DBCPFC was optional.