Peanut allergy and oral immunotherapy

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ABSTRACT

Peanut allergy is the commonest cause of food-induced anaphylaxis in the world, and it can be fatal. There have been many recent improvements to achieve safe methods of peanut desensitisation, one of which is to use a combination of anti–immunoglobulin E and oral immunotherapy. We have treated 27 patients with anti–immunoglobulin E and oral immunotherapy, and report on the outcomes and incidence of adverse reactions encountered during treatment. The dose of peanut protein tolerated increased from a median baseline of 5 to 2000 mg after desensitisation, which is substantially more than would be encountered through accidental ingestion. The incidence of adverse reactions during the escalation phase of oral immunotherapy was 1.8%, and that during the maintenance phase was 0.6%. Most adverse reactions were mild; three episodes were severe enough to warrant withdrawal from oral immunotherapy, but none required epinephrine injection. Preliminary data suggest that unresponsiveness is lost when daily ingestion of peanuts is stopped after the maintenance period.

Hong Kong Med J 2019;25:228–34
https://doi.org/10.12809/hkmj187743

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This article was published on 10 Jun 2019 at www.hkmj.org.

Introduction

Peanut is a leading food allergen alongside shellfish, eggs, milk, beef, and tree nuts.[1] Strict peanut avoidance is difficult and stressful for patients and families. The incidence rates of accidental ingestion can be as high as 50%,[2,3] and it can cause anaphylaxis, which is sometimes fatal. Therefore, new management strategies for peanut allergy are required, such as oral immunotherapy (OIT).

Peanut oral immunotherapy without anti–immunoglobulin E

Most trials on peanut OIT have been conducted in the absence of anti–immunoglobulin E (anti-IgE) pretreatment.[4-10] These studies involve gradually increasing small doses of peanut (escalation phase) up to a maintenance dose of 300 to 4000 mg peanut protein (PP), with or without a phase of rush immunotherapy when several doses were given on the same day at the start of OIT. The daily maintenance dose was then sustained for 6 months to 3 years. Peanut tolerance in subjects increased over time, and the tolerance to peanut in open food challenge (OFC) at completion of the treatment was often more than 2-fold greater than the daily maintenance intake. Efficacy of peanut OIT was high, where 67 % to 93 % of subjects were successfully desensitised to the maintenance dose. These studies have also been considered to demonstrate an acceptable degree of safety although there were dropouts in all the trials. Adverse reaction (AR) rates were 1.2% for build-up doses and 3.7% to 6.3% for home doses. Most ARs were oropharyngeal symptoms but there were some cases of anaphylaxis requiring epinephrine injection. In addition, eosinophilic gastroenteritis was a complication in some patients. In a recent peanut allergy OIT study using defatted slightly roasted peanut flour for desensitisation, 4.3% of children receiving peanut experienced severe ARs compared with <1% of those receiving placebo; 21% of the peanut group withdrew from the study.[10] Further, 14% of those ingesting peanut required epinephrine injection, including one child who experienced anaphylaxis and required three epinephrine injection, compared with 3.2% on placebo.

To sustain non-responsiveness following OIT, Tang et al[7] used a combined therapy of probiotics and peanut OIT. The majority (89.7%) of the probiotics and peanut OIT group were desensitised, and sustained unresponsiveness (SU) was achieved in 87.1% of the children, who could then consume peanuts ad libitum. A related follow-up study indicated that 58% of the probiotics and peanut OIT group subjects achieved 8-week SU at 4 years.[8]

Peanut oral immunotherapy with anti–immunoglobulin E

Prior studies that have combined anti-IgE premedication with OIT are summarised in

Table 1.[11-14] In contrast to other studies, a study conducted in Hong Kong by Lee et al[11] did not have a rush immunotherapy phase (when several doses of peanuts were administered on day 1); instead, peanut dose was increased more gradually at 2-week intervals. Despite differences in study design, the outcomes from all the studies were similar.[11-14] Lee et al[11] found four children tolerated 466 to 4800-fold more PP on OFC than before OIT; their threshold in peanut-specific skin prick tests increased by 10- to 100-fold; and each subject's peanut allergen-specific IgG4 level increased after OIT. The prevalence of ARs in the study by Lee et al[11] appeared to be lower than that first reported by Schneider et al[12] using anti-IgE combined with OIT which included a rush immunotherapy step; however, the Hong Kong population included in the Lee et al study was small.

花生過敏與口服脫敏治療

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花生過敏是目前最常見導致食物誘發過敏性休克的原因，而且可以致命。近年，花生脫敏治療研究的安全度已大有改進，其中一個方案是結合注射抗免疫球蛋白E和口服脫敏治療（OIT）。此項研究中，我們為27名病人進行抗免疫球蛋白E注射和OIT結合治療，並就治療結果和期間不良反應的發生率進行報告。研究發現，患者接受結合治療後，耐受花生蛋白的劑量中位數由5毫克提高至脫敏後2000毫克，這遠遠超於日常意外攝入劑量。在OIT劑量遞增期的不良反應發生率為1.8%；在劑量維持期的不良反應發生率為0.6%。大多數不良反應屬於輕微；當中有三次出現嚴重過敏反應，即使毋須注射腎上腺素但已令患者退出OIT治療。初步數據顯示，在劑量維持期後停止每天攝入花生，對花生的耐受性就會失效。

TABLE 1. Previous studies of peanut OIT with omalizumab

Authors, year, and study type	Subjects	OIT design	Outcomes	ARs
Schneider et al, 2013, open study[12]	n=13, aged 8-16 years	• Omalizumab duration: 20 weeks • OIT started at week 12 • Rush protocol: 6 hrs (up to 250 mg PP) • Escalation: weekly to 2000 mg PP (median 20 weeks) • 12 weeks after stopping omalizumab: DBPCFC of 4000 mg PP and if tolerated ate 10-20 peanuts daily until week 52	• 12 subjects (92%) desensitised to 2000 mg PP daily • 11 subjects (85%) passed DBPCFC of 4000 mg PP • Peanut tolerance increase after OIT: 160-400 fold • Increased PSIgG4 • Decreased PSIgE	• 2% of total peanut doses during escalation • 5 ARs required epinephrine
Lee et al, 2014, open study[11]	n=4, aged 8-12 years	• Omalizumab duration: 16-18 weeks • OIT started at week 12 • Rush protocol: none, but with DBPCFC to determine starting dose • Escalation: bi-weekly to 2000 mg PP (25-31 weeks) • Maintenance: 2000 mg PP for 36 months • OFC 6 months after start of maintenance: 4800 mg PP	• 100% desensitised to 2000 mg PP daily • 75% tolerated 4800 mg PP and 25% tolerated 2800 mg PP in DBPCFC • Peanut tolerance increase after OIT: 466-4800 fold and 10-100 fold in the peanut concentration that elicited a positive SPT, respectively • Increased PSIgG4 and decreased PSIgE	• 0.2% of total peanut doses during escalation • No epinephrine required
MacGinnitie et al, 2017, randomised controlled trial[13]	n=37, 8 placebo and 29 omalizumab	• Omalizumab duration: 19 weeks, subjects who failed to tolerate 1625 mg PP at week 19 received an extra dose of omalizumab at week 20 • OIT started at week 12 • Rush protocol: 1 day (up to 250 mg PP) • Escalation: weekly to 2000 mg PP (median 20 weeks) • 12 weeks after stopping omalizumab: DBPCFC of 4000 mg; if tolerated, continued with 4000 mg PP daily; if failed, challenge continued with 2000 mg PP for an additional 21 weeks	• 23 subjects (79.3%) in omalizumab group tolerated 2000 mg PP 6 weeks after withdrawal of omalizumab vs 1 (12.5%) in placebo group • 22 subjects (75.9%) in omalizumab group passed the 4000 mg OFC vs 1 (12.5%) in placebo group • Peanut tolerance increase after OIT: median 105 fold • Decreased peanut SPT wheal size and increased PSIgE	• AR rate similar between omalizumab and placebo groups; 7.8% vs 16.8% of total doses of PP in omalizumab and placebo groups, respectively • 4 ARs vs 3 ARs required epinephrine in omalizumab and placebo groups, respectively
Yee et al, 2019, open study[14]	n=13, aged 8-16 years	Long-term follow-up study of Schneider et al[12]; subjects received 500 to 3500 mg PP for 67 months	• Decreased peanut SPT PSIgE, Ara h1-IgE, Ara h2-IgE, and PSIgE:IgE ratio • PSIgG4, Ara h1-IgG4, and Ara h2-IgG4 initially increased then decreased • 6 of 13 patients dropped out due to AR. Patients who dropped out had higher month 12 PSIgE and Ara h2-IgE	12 subjects had 257 ARs, mostly mild; 12 of 257 ARs required epinephrine

Abbreviations: AR = adverse reaction; Ara h = *Arachis hypogaea*; DBPCFC = double-blind placebo-controlled food challenge; OFC = oral food challenge; OIT = oral immunotherapy; PP = peanut protein; PSIgE = peanut-specific immunoglobulin E; PSIgG4 = peanut-specific immunoglobulin G4; SPT = skin prick test

Sublingual immunotherapy

Comparisons between studies on sublingual immunotherapy (SLIT) are difficult because different doses and durations.[15-19] However, tentative conclusions can be drawn: in many instances SLIT achieved at least a 10-fold increase in peanut tolerance from baseline after several years of treatment. The ARs experienced during SLIT treatment were mild and consisted mainly of oropharyngeal symptoms. Although SLIT had a better safety profile, OIT appeared to be more efficacious overall.[19]

Epicutaneous immunotherapy

The early trials of epicutaneous immunotherapy (EPIT) were encouraging with at least a 10-fold improvement in tolerated dose following 8 weeks of treatment.[20,21] The safety level was high. The ARs were mostly local and mild and epinephrine injection was not required.

The efficacy, safety, and costs of OIT, SLIT, and EPIT are compared in Table 2.[22] Although it is more efficacious, OIT has greater potential for ARs and is the most costly option, especially if combined with anti-IgE treatment.

Update on the Hong Kong experience

Our centre has now treated 27 peanut-allergic patients aged 6 to 16 years (22 male, 5 female) with anti-IgE and OIT, including the four children previously reported.[11] Patients were considered for anti-IgE and OIT treatment if they were: aged ≥6 years with a history of allergic symptoms developing within 60 minutes of peanut ingestion; serum total IgE between 30 and 1500 IU/mL; a positive skin prick test and/or presence of peanut-specific IgE, and positive oral peanut challenge. They were of good general health with no prior exposure to monoclonal antibodies. Asthma must have been under control, with a forced expiratory volume in 1 second of at least 80% of the predicted value. Systemic glucocorticoids, beta blockers, and angiotensin-converting enzyme inhibitors were prohibited before screening and throughout the study. Aspirin, antihistamines, and antidepressants were not permitted for 3 days, 1 week, and 2 weeks, respectively, before skin testing or oral food challenge. If potential subjects had poorly controlled asthma, poorly controlled atopic dermatitis, or inability to discontinue antihistamines or other medication for skin testing and oral challenges, they were excluded. They were also ineligible if it seemed unlikely that they would comply with the treatment protocol.

The subjects received between 150 and 600 (median 375) mg of anti-IgE for a median of 18 weeks, as determined by baseline serum IgE concentration and body weight.[11] From about 12 weeks after beginning anti-IgE pretreatment, peanuts were eaten daily at home at an initial dose determined by OFC according to our previously reported protocol.[11] Updosing was supervised at bi-weekly intervals in the clinic for 12 to 28 (median 16) weeks (escalation phase) until an oral intake of 2000 mg PP daily was achieved, as previously described in detail.[11] The parents of one child requested to stop escalation after 800 mg of PP because they felt that he was already protected from accidental ingestion and had a strong taste aversion to peanuts. He continued on 800 mg during his maintenance phase. If a patient had a major AR on an updosing visit, the next daily dose was reduced to a previously tolerated dose (often halved), and escalation proceeded more slowly (3-4 weeks) until higher doses were tolerated or the patient withdrew. Successful escalation was followed by a maintenance phase, when patients normally ingested 2000 mg PP daily.

Twenty-three of the 27 peanut allergic children completed the escalation phase according to protocol (85%). There were three dropouts, of which two were caused by peanut-related AR, and the third moved away from Hong Kong for family reasons. Another child stopped updosing at 800 mg, as described

TABLE 2. Comparison of OIT, SLIT, and EPIT for peanut allergy (adapted from reference 22)

	OIT	SLIT	EPIT
Daily maintenance dose (PP)	133-4000 mg	165-3700 μg	50-250 μg
Updosing	Every 1 or 2 weeks	Every 1 or 2 weeks	Initiation and periodic follow-up
Adverse reactions	Mostly minor; some severe	Minor	Minimal
Efficacy	Very good	Good	Ongoing investigation
Desensitisation	Substantial	Moderate	Ongoing investigation
Sustained unresponsiveness	33%-87.1%	10%-100%	ND
Long-term tolerance	Insufficient data	ND	ND
Costs	Expensive (very costly if combined with anti-IgE)	Less costly	ND

Abbreviations: anti-IgE = anti–immunoglobulin E; EPIT = epicutaneous immunotherapy; ND = no data; OIT = oral immunotherapy; PP = peanut protein; SLIT = sublingual immunotherapy

already, but continued into the maintenance phase (Fig). The dose of PP tolerated at OFC increased from a median of 5 mg at baseline to 200 mg after anti-IgE treatment and subsequently to a median of 2000 mg in the maintenance phase. There was a 400-fold improvement in the median tolerated peanut dose (Table 3), yielding a final tolerance greater than the amount of peanuts likely to be encountered through inadvertent ingestion.

The immunological data are shown in Table 3. There was a marked decrease in biomarkers such as peanut-specific IgE and Ara h1, 2, and 3 (but not in Ara h 8 and 9, which were very low at baseline). Skin prick testing (SPT) and the dilution of peanut extract in extinction titration SPT also showed improvements. The level of peanut sIgG4 increased substantially, consistent with the recruitment of an IL-10/Treg pathway.

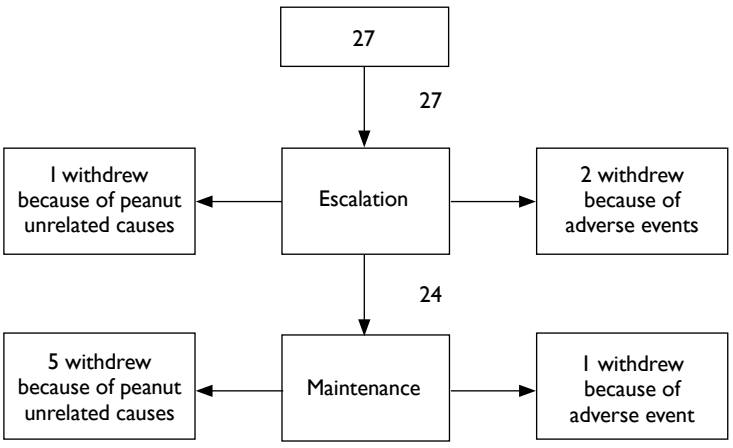

FIG. Number of patients undergoing peanut OIT

Side-effects during peanut oral immunotherapy

Escalation phase

The ARs during updosing in hospital were directly observed; those ARs experienced at home were self-reported by patients' parents. There were 18 observed and 46 reported episodes of AR to 3560 administered doses of peanut (1.8%). Thus, 71.9% of all ARs during the escalation phase occurred at home. One episode could comprise one or more symptoms (Table 4). Most ARs were minor (Table 4) and resolved spontaneously or after administration of an antihistamine. One subject had 12 minor episodes but still completed escalation. There were four major episodes, which involved development of asthma, repeated vomiting, and angioedema (0.1%), and they occurred in two patients who dropped out (Fig).

The frequent occurrence of gastrointestinal symptoms (n=62) is consistent with that reported previously.[14,23]

TABLE 3. Immunological data during peanut OIT*

	Baseline median (n=27)	Post–anti-IgE median (n=27)	Maintenance median	P value (Wilcoxon signed rank test)
Peanut dose (mg)	5 (n=26)†	200	2000 (n=24)	<0.0001‡
Peanut-specific IgE (kU/L)	28	ND	10.5 (n=17)	0.0007
Ara h1-specific IgE (kU/L)	3.5	ND	1.98 (n=17)	0.0015
Ara h2-specific IgE (kU/L)	26.1	ND	7.64 (n=17)	0.0005
Ara h3-specific IgE (kU/L)	0.45	ND	0.21 (n=17)	0.0016
Ara h8-specific IgE (kU/L)	<0.1	ND	<0.1 (n=17)	0.2685
Ara h9-specific IgE (kU/L)	<0.1	ND	<0.1 (n=17)	0.5282
Peanut-specific IgG4 (μg/L)	1118	ND	>50 000 (n=19)	<0.0001
SPT (mm)§	11	6	5.5 (n=24)	<0.0001
Peanut extinction SPTs (dilution)	1000	50	10 (n=24)	<0.0001‡

Abbreviations: Ara h = *Arachis hypogaea* (peanuts); IgE = immunoglobulin E; ND = not done; SPT = skin prick test

* The figures are the values at baseline; about 12 weeks after start of anti-IgE (just before the beginning of OIT) and the most recent results between 2 and 36 months of the maintenance phase depending on the stage the patient had reached. Wilcoxon signed rank test was performed to test paired pre- and post- changes between subjects (P<0.05)

† One family declined a baseline oral peanut challenge because of a history of very severe reactions, so the first challenge was deferred until after 12 weeks of anti-IgE treatment

‡ Comparison of post–anti-IgE data with baseline. All the other P values are comparisons of maintenance data with baseline values

§ SPT wheal size was the mean of the sum of the two longest perpendicular diameters

TABLE 4. Reported ARs during peanut oral immunotherapy

Symptoms*	No. of ARs in escalation phase	No. of ARs in maintenance phase
Gastrointestinal tract†	62	41
Skin‡	22	23
Respiratory tract§	4	18
Eyes‖	7	4

Abbreviation: ARs = adverse reactions

* Several symptoms may occur in combination

† Includes abdominal pain, nausea, vomiting, acid reflux, diarrhoea, lip swelling, itching of lips/mouth/throat, altered taste

‡ Includes hives, rashes, angioedema, itching

§ Includes coughing, rhinitis, wheezing, shortness of breath

‖ Includes itching, redness

Maintenance phase

Twenty-four patients entered the maintenance phase of OIT (Fig). The duration of their maintenance phases so far has ranged from 2 to 42 (median 24) months. One child planned to study overseas and therefore continued on the maintenance doses for 6 months longer than planned (42 months in total) until he returned to Hong Kong for holidays. All parents and patients were asked to report any AR.

To date, there have been 80 reported episodes of AR from 14 350 administered doses (0.6%). The majority of subjects had no ARs, and 85% of all the ARs reported were experienced by seven (29.2%) patients. Six of these patients were able to continue with OIT, but one patient withdrew because of severe eczema.

Forty-one, 23, and 18 side-effects reported during the maintenance phase were related to the gastrointestinal tract, skin, and respiratory system, respectively; thus, gastrointestinal symptoms predominated again (Table 4). The gastrointestinal symptoms were mostly mild and resolved either spontaneously or after antihistamine administration. Occasionally, it was also necessary to administer an oral anti-spasmodic drug.

While the incidence of AR during the maintenance phase of OIT was very low, repeated ARs still occurred in some subjects, and one episode was severe enough to warrant withdrawal from the programme. This highlights the importance of continued vigilance throughout OIT.

Dropouts

Four patients left Hong Kong for family reasons. Another two patients (twins) developed unexplained intermittent mild neutropenia after 2 years of maintenance OIT, which was not caused by peanuts. Nonetheless, although they stopped daily peanut consumption, they continued to be monitored to assess for SU. Two children were withdrawn during escalation, and one dropped out during maintenance because of peanut allergy related to AR during OIT (Fig). Thus, overall, one-third of subjects dropped out (9 of 27), but only one-third of the dropouts (3 patients; 11.1%) withdrew because of AR caused by peanut ingestion.

The incidence of AR in our subjects was similar[5,9,24] or even lower than that in previous reports.[6,8,10,25,26] Baseline allergic rhinitis and peanut SPT wheal sizes have been suggested to be significant predictors of higher overall rate of AR during peanut OIT,[23] but in our series, baseline peanut SPT results; extinction dilution SPTs; peanut-specific IgE; *Arachis hypogaea* 1-, 2-, 3-, 8-, and 9-specific IgE concentrations; and the presence of rhinitis and asthma were not predictors of ARs (P>0.05 for all correlations).

Preliminary data on sustained unresponsiveness

A major concern regarding immunotherapy is whether it can induce long-term tolerance. Seven of our patients have been followed up after cessation of daily peanut consumption. Three of these subjects discontinued peanut ingestion after maintenance treatment with 1600 to 2000 mg PP daily, and their sensitivity returned, as evidenced by ARs to intentional or accidental ingestion of peanuts as well as ARs to 100 mg and 400 mg PP upon OFC at 6 months (n=2) and 12 months (n=1), respectively. The other four subjects have continued to ingest their maintenance doses of peanuts 3 times weekly after the maintenance phase was completed and have not experienced any ARs after 4, 7, 8, and 24 months of observation, respectively.

Syed et al[27] randomised 43 subjects aged 4 to 45 years to receive peanut OIT (n=23) or placebo (n=20). Peanut doses were escalated to 4000 mg PP and maintained for 24 months. Then, subjects avoided peanuts for 3 months, and their SU was assessed. In all, 87% of the subjects were successfully desensitised to 4000 mg PP, and 30% achieved SU after avoiding peanuts for 3 months. Of the seven subjects who had SU at 3 months, only three of them (13% of the treatment group) still achieved SU at 6 months of peanut avoidance.

Conclusions

Our protocol of combining anti-IgE with OIT is efficacious and safe, with only minor side-effects encountered by most patients. This is a retrospective record review and therefore is an audit of our real-world experience. There is growing momentum behind the development of commercial products for peanut desensitisation,[9,10,21] and it is essential to compare their efficacy and safety with existing

techniques for peanut immunotherapy in a real-world situation.[28-30]

Selection of suitable patients to undergo OIT is critical, as it is a labour-intensive and expensive treatment that requires time, patience, and compliance from everyone involved. We spend much time explaining the procedure in detail to the family and child to ascertain whether they are likely to complete the treatment. The patient or the patient's parent (if the patient is a child) signs an informed consent form if they agree to proceed. If they have concomitant asthma, we ensure that this is optimally controlled before embarking on OIT. Even with careful selection, four of our subjects left Hong Kong for family reasons before OIT was completed. This was unavoidable but nevertheless undesirable for the continuity of their treatment. Any treatment that takes years to complete will always be a challenge, especially for families whose children relocate for study, work, or other reasons. While some treatments can be continued by centres overseas, OIT expertise is not so easily accessible, and it may be necessary to discontinue treatment. This is regrettable, as all the parents and patients, who completed their desensitisation programmes successfully reported that their quality of life had been improved.

We recommend that this treatment only be offered by specialists with the appropriate training within an environment with immediate resuscitation facilities and support staff who are trained to manage allergic emergencies and can undertake patient education.

Our experience suggests that peanut sensitivity will likely return after a few months when OIT is stopped, so regular ingestion of peanut consumption is required to sustain the desensitised state. We now advise patients to continue consuming the maintenance dose of peanuts at least 3 times weekly to sustain desensitisation. They are seen every 6 months for skin testing, and they undergo a formal peanut challenge annually or more frequently, according to clinical judgment. We also advise that they retain their epinephrine autoinjectors for emergency treatment of unexpected events.

Alternative methods that hold promise for peanut desensitisation are being developed, including SLIT,[15-18,20] low-dose OIT without anti-IgE,[6,9,31] co-administration of a probiotic[7,8] with OIT to promote longer-term tolerance, and EPIT.[21] Thus additional transformative treatments for peanut and other food allergies will be forthcoming in the near future.

Author contributions

All authors contributed to the design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision for important intellectual content. All authors also had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics approval

The study was approved by the Hong Kong Sanatorium & Hospital Research Committee (Ref RC-2018-27). Patients provided informed consent.

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