Immunotherapy for peanut allergy

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ABSTRACT

Peanut allergy is one of the commonest food hypersensitivities causing fatal or near-fatal reactions. There is, currently, no preventive treatment and the incidence of severe allergic reactions during peanut desensitisation has limited its clinical use. Anti–immunoglobulin E therapy has been shown to be effective in preventing peanut-induced reactions but it does not result in long-term tolerance. Two important advances have recently been reported. One involves gradual oral introduction of peanut protein to desensitise, whereas the other approach uses a combination of anti–immunoglobulin E and oral peanut immunotherapy. Both approaches could offer a way to desensitise with a far greater margin of safety than has, hitherto, been reported. This article provides an overview of the literature on peanut immunotherapy and describes the experience in a small group of children in Hong Kong who were treated successfully using anti–immunoglobulin E combined with oral peanut desensitisation.

Hong Kong Med J 2014;20:325–30
DOI: 10.12809/hkmj144243

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This article was published on 20 Jun 2014 at www.hkmj.org.

Introduction

Peanut allergy is the commonest food hypersensitivity causing fatal or near-fatal reactions in the western world.[1] There has been a longstanding but erroneous belief that peanut allergy is less prevalent in Hong Kong compared with other countries. Two studies have estimated the prevalence of allergic reactions after eating peanuts in children living in Hong Kong to be 0.6% and 0.3%, respectively,[2,3] which is similar to pooled international data. Strikingly, 700/100 000 of the population in Hong Kong aged 14 years or younger is estimated to have a risk of anaphylaxis[3] and peanut is a leading causative food allergen alongside shellfish, egg, milk, beef, and tree nuts.[2,3]

The current medical management of peanut allergy is to encourage strict avoidance of peanuts and to use self-administered adrenaline for anaphylaxis due to inadvertent ingestion. Dietary restrictions are not only difficult but also stressful for the patient and families. Reactions from accidental exposure are common and annual incidence rates range from 3% to 50%.[4] Furthermore, adrenaline is not always accessible for emergency use. It is, therefore, essential to discover ways to prevent allergic reactions caused by peanut exposure. While herbal remedies may show some promise,[5,6] most of the previous studies have tested the efficacy and safety of desensitisation.

Food desensitisation means an increase in threshold of food antigen causing allergic symptoms and depends on the regular (usually daily) consumption of the food. When dosing is interrupted, any protective effect may be lost or attenuated. Mechanisms for desensitisation include decreased allergen-specific immunoglobulin E (IgE), increased allergen-specific IgG4, and reduced responsiveness of mast cells and basophils. In established oral tolerance, the food can be eaten without allergic problems even when regular dosing ceases. Mechanisms responsible for oral tolerance likely involve recruitment of regulatory T cells with a shift away from the pro-allergic T helper cell subtype 2 (TH2) phenotype. There is scant information on long-term outcomes and tolerance following oral immunotherapy (OIT) in food allergy.

Previous immunotherapy trials

There are no immunotherapy regimens in routine use for peanut allergy. Most (but not all) peanut immunotherapy protocols involve an initial escalation phase (range, 0-7 days) of orally administered peanut, or a pre-immunotherapy oral peanut challenge, to determine the starting dose for OIT. This is followed by administration of further build-up doses (range, 0-22 months) and then maintenance doses (range, 1-36 months).

The maximum maintenance doses are between 300 mg and 4000 mg peanut protein. While some studies have shown encouraging results,[7-12] the risk of severe reactions during peanut OIT is of concern.

Clark et al[7] reported that four children underwent successful peanut OIT starting from

花生過敏症的免疫治療

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花生過敏症是其中一種最常見的食物過敏，可導致嚴重甚至致命的過敏反應。現時尚未有方法能有效預防，而由於花生脫敏治療有可能引起嚴重過敏反應，因此其臨床應用有一定限制。抗免疫球蛋白E治療證實能有效減低花生所引起的過敏反應，但未能帶來長遠的耐受作用。醫學界最近研發出兩種嶄新的花生過敏治療：一是以遞增方式口服花生蛋白進行脫敏治療；另一種是綜合使用抗免疫球蛋白E治療及口服花生免疫治療。兩種療法的安全系數均遠高於現有數據，能增強患者的耐受能力，安全有效。本文將概述花生免疫治療的發展，並分享數個本港兒童患者的成功個案，闡述其接受抗免疫球蛋白E值治療及口服花生免疫治療的臨床經驗。

5 mg peanut protein to reach a maintenance dose of 800 mg peanut protein after 12 biweekly increments. During the final open challenge, all four subjects could ingest between 2380 mg and 2760 mg peanut protein reflecting an increase in dose threshold of at least 48-478 fold. Hofmann et al[8] showed that 20 of 28 subjects were able to complete peanut OIT to reach a daily maintenance dose of 300 mg. Jones et al[9] showed that 27 of 29 subjects with peanut allergy could be desensitised. Before OIT, they were developing reactions to eating less than 50 mg peanut protein but after 4 to 22 months of daily maintenance dosing with 300 mg, they were able to ingest 3900 mg. Similarly, Blumchen et al[10] reported successfully desensitising 14 of 23 subjects with OIT to reach a maintenance dose of 500 mg peanut. Anagnostou et al[11] reported successful desensitisation in 19 of 22 patients. Thirty weeks into the maintenance phase of OIT and ingesting 800 mg peanut protein daily, the subjects could eat a mean dose of peanut that was 1000-fold greater than baseline. Varshney et al[12] published the first double-blind placebo-controlled study of peanut OIT and showed that 16 of 19 subjects were able to consume 4000 mg after 12 months of OIT.

In these reports, while allergic symptoms were uncommon during maintenance dosing (2.1%-3.7% of doses), they were very common during the initial escalation phase (47%-100% of patients) and the build-up phase (1.2%-46% of doses).[7-12] Up to 10.5% of the subjects required adrenaline treatment on the initial escalation day. The dropout rate was high (4.5%-10.7%) due to the severity of allergic complications. These problems have greatly restricted the use of oral peanut desensitisation.

Use of sublingual immunotherapy (SLIT) may hold promise but there is limited experience with this form of desensitisation in peanut allergy. Kim et al[13] successfully desensitised 18 children with peanut allergy using SLIT over 12 months. As assessed by double-blind placebo-controlled food challenges, the treatment group was able to ingest 20 times more peanut protein compared with the placebo group (median, 1710 vs 85 mg peanut protein). In 2013, Fleischer et al[14] showed that after 44 weeks of SLIT, 14 out of 20 peanut-allergic subjects showed increased ability to ingest peanut protein from 3.5 mg to 496 mg; and after 68 weeks of SLIT, the increase was twice as high at 996 mg. Allergic symptoms developing during SLIT were reported with 11.5% of peanut doses and 8.6% of placebo doses. Of the 4182 active peanut doses, only 0.26% of the doses taken at home required antihistamine treatment and 0.02% required use of salbutamol. Thus, with the limited data available, SLIT appeared to have fewer allergic side-effects than OIT.

Anti-IgE administration has the potential to prevent peanut allergy,[15,16] as it reduces free-circulating IgE levels and inhibits expression of the high-affinity IgE receptor on mast cells and other immune cells.[17-20] Leung et al[15] showed that 450 mg of a humanised IgG1 monoclonal antibody against IgE significantly increased the threshold of sensitivity to peanut on oral food challenge from approximately half a peanut to almost nine peanuts. Similarly, Sampson et al[16] have suggested that the anti-IgE monoclonal antibody omalizumab (Xolair; Novartis, Basel, Switzerland), which is approved in Hong Kong and in many other countries for treating severe asthma, could increase the tolerability to peanut. Unfortunately, this latter study was terminated early because of two severe anaphylactic reactions after oral peanut challenge during the recruitment phase.

These results are encouraging but Xolair has to be administered by subcutaneous injection. As the dose and frequency of administration are determined by total serum IgE and body weight, it is suited optimally for only those within 20% of the ideal body weight. Furthermore, the drug is expensive and peanut allergy relapses soon after anti-IgE is discontinued; thus, it cannot induce long-term tolerance, which may likely require specific allergen immunotherapy.

Recent developments

There have been some recent advances in peanut OIT that look promising. Anagnostou et al[21] conducted a randomised controlled cross-over trial comparing OIT using peanut flour with peanut avoidance. They reported successful OIT in 62% of a group of children aged 7 to 16 years with peanut allergy. There was an initial updosing schedule of biweekly increments up to a maximum oral intake of 800 mg peanut protein/day. This was followed by a maintenance period when the highest dose that could be safely eaten was taken daily for 26 weeks. By this time, 91% could ingest 800 mg peanut protein daily versus none in the control group, and 54% had no reactions to a 1400 mg peanut challenge. Side-effects were reported in 20% of subjects but

they were mostly mild consisting mainly of gastro-intestinal symptoms and oral pruritus. The median peanut threshold dose had increased by 25.5-fold.

In light of the biological activities of Xolair, it was logical to combine it with peanut OIT to test whether the drug can facilitate allergen-specific desensitisation by reducing incidence of side-effects. A period of pretreatment with anti-IgE has already been reported to decrease acute allergic reactions developing during rush immunotherapy for ragweed-induced seasonal rhinitis and milk allergy.[22,23]

Schneider et al[24] treated 13 children with a brief course of Xolair over 20 weeks. At 12 weeks of Xolair administration, OIT was started. On the first day of OIT, 11 desensitising doses of peanut flour were given over 6 hours (rush OIT). This was followed by a slower escalation phase of peanut allergen doses at weekly intervals for 7 to 12 weeks until the subjects were receiving 4000 mg of peanut flour (equivalent to about 9-10 peanuts) daily at which time Xolair was discontinued. The children then continued to ingest 4000 mg peanut flour daily during maintenance phase. On this regimen, the subjects were able to ingest 160 to 400 times the dose that could be eaten before OIT. The rapidity with which the patients reached 4000 mg was notable and this was achieved with only about 2% of the peanut doses associated with mild allergic reactions. The initial rush desensitisation allowed the patients to ingest a cumulative dose of 992 mg peanut flour (about 2 peanuts) after only 24 hours of OIT. This would have removed the patient very rapidly from risk of anaphylaxis caused by accidental exposure.

Schneider et al's report[24] is very similar to our experience in Hong Kong. We have completed the first phase of a small pilot desensitisation study in four children with mild-to-moderately severe peanut allergy in which Xolair and peanut OIT were combined. The inclusion criteria for the study were volunteers aged 8 years or older with a history of peanut allergy manifested by any of the following: urticaria, angioedema, asthma, gastro-intestinal symptoms, or anaphylaxis within 60 minutes of ingestion; a serum total IgE between 30 and 1500 IU/mL; a positive double-blind placebo-controlled oral peanut challenge; good general health; within 20% of ideal body weight; a positive skin prick test (at least 3 x 3 mm wheal greater than diluent control); a positive serum-specific IgE to peanut as measured by radioallergosorbent test (RAST); and no prior exposure to monoclonal antibodies. Asthma must have been stable with a forced expiratory volume in 1 second of at least 80% 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 patients had poorly controlled asthma and/or atopic dermatitis, or inability to discontinue antihistamines or other medications for skin testing and oral challenges, they were excluded. They were also deemed ineligible if it seemed unlikely that they would be able to comply with the study protocol for any reason. The subjects were recruited from patients attending the Allergy Centre at the Hong Kong Sanatorium and Hospital. The study was approved by the Hospital Research Ethics Committee; both written informed consent from the children's parents and the children's informed verbal assent were obtained. The inclusion and exclusion criteria for the previous trials cited in this review are included in Table 1[7-14,21,24] for comparison.

The children in our study had a history of peanut allergy manifested by urticaria, angioedema, asthma, sore mouth, and anaphylaxis within minutes of ingestion (Table 2). Their serum total IgE levels were raised and they had a positive skin prick test and RAST to peanut. They were also positive for specific IgE to Ara h 2, a molecular component of peanut protein which, at high levels, is reported to identify a subgroup of subjects allergic to peanut with more severe symptoms, although this issue is considered debatable.[25] Each child had a positive, double-blinded oral peanut challenge at recruitment confirming their clinical allergy.

The study protocol had three stages. In stage 1, each subject received Xolair for 16 to 18 weeks. At 12 weeks of Xolair treatment, each subject had a graded oral peanut challenge to ensure that Xolair had increased the amount of peanut protein that could be ingested. If the challenge showed at least a two-step increase in the threshold dose of peanut provoking a reaction compared with baseline, OIT was started. If the increase in threshold was less than two-dose steps, the peanut challenge was repeated 4 weeks later to ensure that the threshold target had been met before OIT was initiated; if not, the subject was withdrawn. In stage 2, OIT had an escalation phase of peanut oral administration with updosing at biweekly intervals. In the most sensitive subjects, the doses could be: 0.5, 1, 2, 5, 12, 25, 50, 100, 200, 400, 800, 1200, 1600, and 2000 mg of peanut protein, given as defatted peanut flour with 50% peanut protein by weight. However, if subjects became less sensitised to peanut during Xolair treatment, as was the case in all our four subjects, the escalation phase might start in the mid-range of the dose range indicated above, thus, shortening the escalation phase considerably. The escalation phase was followed by maintenance phase when subjects continued to ingest the top dose of peanut (4000 mg peanut flour) for 36 months. Stage 3 was started when OIT ceased after 36 months and subsequent progress was monitored to assess whether long-term

TABLE 1. Indications and contra-indications for oral and sublingual immunotherapy in previous trials for peanut allergy

Trial	Therapy*	Indications†
Clark et al[7]	OIT	9-13 Years old Positive DBPCFC to peanut
Hofmann et al[8]	OIT	1-16 Years old Peanut-specific IgE >15 kU/L, or >7 kU/L with clinical reaction within the past 6 months in children >2 years old, or >7 kU/L for children <2 years old Positive SPT ≥3 mm vs negative control
Jones et al[9]	OIT	1-16 Years old Peanut-specific IgE ≥15 kU/L, or ≥7 kU/L with clinical reaction within the past 6 months Positive SPT ≥3 mm vs negative control
Blumchen et al[10]	OIT	>3 Years old Peanut IgE >0.35 kU/L Positive DBPCFC to peanut
Anagnostou et al[11]	OIT	4-18 Years old Positive peanut-specific IgE Positive SPT ≥3 mm vs negative control
Varshney et al[12]	OIT	1-16 Years old Positive peanut-specific IgE >15 kU/L, or >7 kU/L with significant reaction within 6 months Positive SPT ≥3 mm vs negative control
Kim et al[13]	SLIT	1-11 Years old Peanut-specific IgE ≥7 kU/L
Fleischer et al[14]	SLIT	12-40 Years old Peanut-specific IgE ≥0.35 kU/L Positive SPT ≥3 mm vs negative control Positive DBPCFC to peanut
Anagnostou et al[21]	OIT	7-16 Years old Positive SPT ≥3 mm vs negative control Positive DBPCFC to peanut
Schneider et al[24]	OIT	7-25 Years old Positive DBPCFC to peanut Total IgE >50 to <2000 kU/L Peanut-specific IgE >20 kU/L Positive SPT ≥6 mm vs negative control

Abbreviations: DBPCFC = double-blind placebo-controlled food challenge; IgE = immunoglobulin E; OIT = oral immunotherapy; SLIT = sublingual immunotherapy; SPT = skin prick test

* Contra-indications for OIT/SLIT included: major chronic illness; pregnancy; a history of severe, life-threatening anaphylaxis (with hypotension) to peanut; severe or poorly controlled asthma; poorly controlled atopic dermatitis; and any medical condition preventing a food challenge, skin testing, and/or complying with study protocol

† Another indication in all studies is a clinical history of reaction to peanut within 60 minutes of ingestion

tolerance had been induced over the next 36 months (end of stage 3). Our study subjects are in stage 2 of the pilot study.

The Hong Kong protocol differed from Schneider et al's[24] in some respects. We treated the children with Xolair for 16 to 18 weeks and not 20 weeks. The Xolair treatment only overlapped the initial few weeks of OIT in the Hong Kong subjects whereas in Schneider's protocol, Xolair was administered during the entire build-up phase of OIT. The serum elimination half-life of Xolair averaged about 26 days, so even when the injections were stopped, the drug effect would likely have persisted significantly longer. We did not have a rush OIT phase, preferring to updose more slowly at biweekly intervals to give a wider margin of safety. As a consequence, the duration of our escalation phase was slightly longer (14 weeks) compared with 7 to 12 weeks in the Schneider et al's study.[24] Despite these differences in protocol design, the results were very similar between the two studies.

One subject (subject 1) experienced mild abdominal cramps and mild oral itching when eating 4000 mg peanut flour (2000 mg peanut protein; equivalent to about 9 peanuts as each peanut contains about 240 mg peanut protein) as a single daily dose at home, but was able to ingest the dose when administered in two 2000 mg doses separated by at least 30 minutes. Compared with baseline, when subjects could only eat 2 to 12 mg peanut flour, at the end of the escalation phase on formal challenge under supervision, three subjects could eat a cumulative maximum dose of 9600 mg peanut flour (about 20 peanuts) [Table 2]. Subject 1 could eat a cumulative dose of 5600 mg (about 11 peanuts) but reacted at 9600 mg with mild abdominal cramps which resolved spontaneously. On the combination regimen, the children were, therefore, able to eat between 466- and 4800-fold more peanut protein than before they were desensitised. Subjects'

TABLE 2. Characteristics, IgE, IgG4, FEV_1, and peanut sensitivity (skin testing and oral challenge) before and following omalizumab (Xolair, Novartis) combined with oral peanut immunotherapy in four subjects

Characteristic	Subject No.			
	1	2	3	4
Age (years)	12	8	9*	9*
Sex	M	F	M	M
FEV_1 (% predicted)	83	93	99	102
Total IgE (kU/L)	759	560	240	660
Symptoms induced by peanut ingestion	As, U, Ang, An	Ang	As	Sm
Peanut sensitivity				
Baseline SPT wheal size to undiluted peanut allergen (ALK-Abelló, Hørsholm, Denmark) [mm]	9 x 8	15 x 13	14 x 6	15 x 12
Baseline extinction titration of SPT (dilution of allergen)	1:1000	1:5000	1:5000	1:500 000
End of updosing phase for allergen (dilution of allergen)	1:100	1:500	1:50	1:5000
Peanut oral challenge				
Cumulative tolerated dose at baseline (peanut flour in mg)	12	12	2	2
Cumulative tolerated dose at end of updosing phase for allergen (peanut flour in mg)	5600	9600	9600	9600
Peanut-specific IgE and IgG4†				
Baseline peanut-specific IgE kU/L (RAST score)	23.4 (4)	2.62 (2)	6.60 (3)	2.06 (2)
Baseline Ara h 2–specific IgE kU/L (RAST score)	16.5 (3)	2.54 (2)	4.32 (3)	0.9 (2)
Peanut-specific IgE at end of updosing phase for allergen kU/L (RAST score)	61.8 (5)	2.33 (2)	22.7 (4)	5.17 (3)
Baseline peanut-specific IgG4 (μg/L)	8056	398	1700	851
Peanut-specific IgG4 at end of updosing phase for allergen (μg/L)	40 016	413	8049	3633
Omalizumab dose and frequency‡	375 mg (every 2 weeks)	300 mg (every 4 weeks)	225 mg (every 4 weeks)	450 mg (every 4 weeks)
No. of omalizumab injections	9	5	5	5
No. of weeks (visits) to complete omalizumab and peanut updosing to reach maximum maintenance dose of 4000 mg peanut flour	28 (14)	25 (10)	25 (10)	31 (12)

Abbreviations: An = anaphylaxis; Ang = angioedema; As = asthma; FEV_1 = forced expiratory volume in 1 second; IgE = immunoglobulin E; IgG4 = immunoglobulin G4; RAST = radioallergosorbent test; Sm = sore mouth; SPT = skin prick test; U = urticaria

* Twins

† IgE RAST for peanut and Ara h 2 were assayed by ImmunoCAP; Phardia (Pharmacia Diagnostics): RAST score for specific IgE: 1 = 0.35-0.69 kU/L; 2 = 0.70-3.49 kU/L; 3 = 3.5-17.4 kU/L; 4 = 17.5-52.4 kU/L; 5 = 52.5-99.9 kU/L; 6 = ≥100 kU/L; IgG4 was assayed by Immulite 2000; Siemens Medical Diagnostic

‡ Omalizumab dose was given as recommended by Novartis' guidelines. Peanut protein constitutes 50% of peanut flour (w:w). The tests at end of updosing were conducted 2 weeks after the maintenance dose had been reached

threshold skin prick test reactions to peanut extract had also increased (10-100 fold) [Table 2]. Thus, at the end of the escalation phase, all the children could ingest many more peanuts than would have been eaten inadvertently, and were protected from severe allergic reactions after accidental ingestion.

The clinical improvement was accompanied by an increase in each subject's peanut-specific IgG4, suggesting mechanistic recruitment of the interleukin-10/Treg pathway and a shift away from the pro-allergic TH2 phenotype. It was noted that serum peanut-specific IgE increased in three out of the four children following Xolair and updosing of allergen, when concentrations might have been expected to decrease, as in other forms of allergen-specific desensitisation (Table 2). Interpretation of IgE measurements following Xolair administration is difficult because the drug complexes with free-circulating IgE resulting in an apparent increase in total IgE levels that may last for many weeks after treatment.[26] Measurement of free-serum IgE would circumvent this problem but this is technically difficult to assay and was not performed in our laboratory. Instead, we used extinction skin prick tests as a surrogate marker of mast cell-bound peanut-specific IgE.

The incidence of side-effects during desensitisation in our limited experience was 0.2% of total number of peanut doses, which is much less than the incidence reported previously in the absence of Xolair cover[7-12] and even less than the 2% reported recently.[24]

Conclusion

The results of recent studies taken together are encouraging and strongly suggest that there are several new strategies, including the use of anti-IgE with OIT, that could now allow desensitisation to peanut to be undertaken safely and, in one study, very rapidly. These approaches may have merit in the future for treating severe peanut allergy once protocols have been refined and results validated. However, these treatment regimens should always be used by experienced and appropriately trained clinicians, in an environment where facilities are available for emergency resuscitation in case a serious adverse event occurs. Whether the regimens can induce long-term tolerance will have to await review of progress when OIT ceases after 3 years.

Acknowledgements

The authors thank The Hong Kong Sanatorium and Hospital for support and to the study steering group (Dr YC Tsao, Dr Walton Li, Prof Raymond Liang, Prof Kar-nang Lai, Dr Edmond Ma, and Dr Stephen Till) for advice. We also thank Ms Melissa Tung for secretarial assistance.

Declaration

No conflicts of interests were declared by authors.

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