A B S T R A C T
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.

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 al7 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...
immunotherapy step; however, the Hong Kong anti-IgE combined with OIT which included a rush more than that first reported by Schneider et al.12 using peanut allergen-specific IgG4 level increased after OIT. The prevalence of ARs in the study by Lee et al.13 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.

### TABLE 1. Previous studies of peanut OIT with omalizumab

<table>
<thead>
<tr>
<th>Authors, year, and study type</th>
<th>Subjects</th>
<th>OIT design</th>
<th>Outcomes</th>
<th>ARs</th>
</tr>
</thead>
</table>
| Schneider et al, 2013, open study12 | 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 PSIgG4 | • 2% of total peanut doses during escalation  
• 5 ARs required epinephrine |
| Lee et al, 2014, open study11 | 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 trial13 | 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 study14 | n=13, aged 8-16 years | Long-term follow-up study of Schneider et al; subjects received 500 to 3500 mg PP for 67 months | • Decreased peanut SPT PSIgE, Ara h1-IgE, Ara h2-IgE, and PSIgE:lgE 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

香港醫學雜誌 | Volume 25 Number 3 | June 2019 | www.hkmj.org
Sublingual immunotherapy

Comparisons between studies on sublingual immunotherapy (SLIT) are difficult because different doses and durations. 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.

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. 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. 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. 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. 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. 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. 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.

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

<p>| TABLE 2. Comparison of OIT, SLIT, and EPIT for peanut allergy (adapted from reference 22) |
|______________________________________<strong><strong>|</strong></strong>___________<strong>|</strong>_____________| |</p>
<table>
<thead>
<tr>
<th>OIT</th>
<th>SLIT</th>
<th>EPIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily maintenance dose (PP)</td>
<td>133-4000 mg</td>
<td>165-3700 µg</td>
</tr>
<tr>
<td>Updosing</td>
<td>Every 1 or 2 weeks</td>
<td>Every 1 or 2 weeks</td>
</tr>
<tr>
<td>Adverse reactions</td>
<td>Mostly minor; some severe</td>
<td>Minor</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Very good</td>
<td>Good</td>
</tr>
<tr>
<td>Desensitisation</td>
<td>Substantial</td>
<td>Moderate</td>
</tr>
<tr>
<td>Sustained unresponsiveness</td>
<td>33%-87.1%</td>
<td>10%-100%</td>
</tr>
<tr>
<td>Long-term tolerance</td>
<td>Insufficient data</td>
<td>ND</td>
</tr>
<tr>
<td>Costs</td>
<td>Expensive (very costly if combined with anti-IgE)</td>
<td>Less costly</td>
</tr>
</tbody>
</table>

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.

**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.\(^{14,23}\)

![FIG. Number of patients undergoing peanut OIT](image-url)

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**TABLE 3. Immunological data during peanut OIT**

<table>
<thead>
<tr>
<th></th>
<th>Baseline median (n=27)</th>
<th>Post–anti-IgE median (n=27)</th>
<th>Maintenance median</th>
<th>P value (Wilcoxon signed rank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut dose (mg)</td>
<td>5 (n=28)†</td>
<td>200</td>
<td>2000 (n=24)</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Peanut-specific IgE (kU/L)</td>
<td>28</td>
<td>ND</td>
<td>10.5 (n=17)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Ara h1-specific IgE (kU/L)</td>
<td>3.5</td>
<td>ND</td>
<td>1.98 (n=17)</td>
<td>0.0015</td>
</tr>
<tr>
<td>Ara h2-specific IgE (kU/L)</td>
<td>26.1</td>
<td>ND</td>
<td>7.64 (n=17)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Ara h3-specific IgE (kU/L)</td>
<td>0.45</td>
<td>ND</td>
<td>0.21 (n=17)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Ara h8-specific IgE (kU/L)</td>
<td>&lt;0.1</td>
<td>ND</td>
<td>&lt;0.1 (n=17)</td>
<td>0.2685</td>
</tr>
<tr>
<td>Ara h9-specific IgE (kU/L)</td>
<td>&lt;0.1</td>
<td>ND</td>
<td>&lt;0.1 (n=17)</td>
<td>0.5282</td>
</tr>
<tr>
<td>Peanut-specific IgG4 (µg/L)</td>
<td>11118</td>
<td>ND</td>
<td>&gt;50 000 (n=19)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SPT (mm)§</td>
<td>11</td>
<td>6</td>
<td>5.5 (n=24)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peanut extinction SPTs (dilution)</td>
<td>10000</td>
<td>50</td>
<td>10 (n=24)</td>
<td>&lt;0.0001†</td>
</tr>
</tbody>
</table>

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
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 similar4,6,23 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 al27 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 desensitisation3,10,21 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 peanut desensitisation and modulation of the allergic response. J Allergy Clin Immunol 2011;127:654-60.


