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Sublingual vs Oral Immunotherapy for Food Allergy:

Identifying the Right Approach

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Abstract

The incidence of food allergy in developed countries has increased in recent years, escalating the need to find a suitable form of treatment as an alternative to current management, which includes strict avoidance and ready availability of injectable epinephrine (adrenaline). Allergen immunotherapy is currently being studied for use in the treatment of IgE-mediated food allergy to the most common foods, including peanut, tree nut, milk and egg. Two modalities, oral immunotherapy (OIT) and sublingual immunotherapy (SLIT), have shown great promise. Both OIT and SLIT have been able to desensitize subjects to varying degrees, but the two treatment methods differ in doses that can be achieved, duration of treatment, safety profile and ease of use outside the research setting, among other aspects. More research is needed to conclude which mode of treatment is more effective in inducing long-term tolerance with the least amount of serious adverse reactions. However, OIT and SLIT show great promise, and a widespread treatment for food allergy may be within reach.

1. Food Allergy Background and Epidemiology

Food allergy is defined as a reproducible, immune-mediated, adverse reaction that occurs after exposure to a particular food. The most common foods to elicit reactions include milk, egg, peanut, tree nut, wheat, soy, fish and shellfish.^[1] The incidence of food allergy has increased in recent years. The Centers of Disease Control and Prevention in 2008 reported an 18% increase in food allergy prevalence among American children from 1997 to 2007, with 3.9% being affected.^[2] The rates of self-reported peanut allergy more than tripled from 0.4% in 1997 to 1.4% in 2008.^[3]

The current management of food allergy includes strict dietary avoidance with ready access to self-injectable epinephrine (adrenaline).^[1] Despite this, food allergy continues to be the leading cause of anaphylaxis requiring medical management in both children and adults.^[4] Fatalities from food-induced anaphylaxis were greatest with peanut and tree nut ingestion and were highest among adolescents and young adults.^[5–7]

2. Treatment Strategies

Allergen immunotherapy is a form of treatment in which small doses of allergen are given to the subject and increased over time in order to induce immunological changes. The mechanisms that are used to achieve these changes have only begun to be fully understood.^[8] In general, T helper (T_H)-2 lymphocytes produce interleukin (IL)-4, IL-5 and

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IL-13 cytokines, which promote the activity of mast cells, basophils and eosinophils, the predominant effector cells causing allergic inflammation. Immunotherapy skews effector T cells to increase T-regulatory cell production, which suppresses T_H2-lymphocytes, mast cells, basophils, eosinophils and allergen-specific IgE production, and promotes the production of allergen-specific IgG4.^[9] It is an established treatment in the subcutaneous injection form for the treatment of IgE-mediated allergic rhino-conjunctivitis, allergic asthma and insect venom hypersensitivity.

More recently, sublingual forms of treatment are being used for treatment of allergic rhinitis and allergic asthma due to inhalant allergens in Europe and Asia. The mechanisms of action of sublingual forms of immunotherapy are thought to be similar to the subcutaneous route, as they share similar effects on IgE, IgG4, T-regulatory cell and T_H2 lymphocyte production.^[9] It has been proposed that sublingual treatment affords the added advantage of using oral mucosal dendritic and Langerhans cells to promote production of T-regulatory cells and effector cytokines, i.e. IL-10.

2.1 Past Attempts

In the past, there have been many attempts to treat food allergies. However, aside from case reports, attempts to develop widely successful methods of treatment have failed. During the 1990s, subcutaneous immunotherapy with peanut extract was attempted in peanut allergic adults in a placebo-controlled trial.^[10,11] In that study, all treated adults underwent rush injection immunotherapy, followed by a maintenance injection phase. All subjects in the treatment arm finished rush immunotherapy, increased their double-blind, placebo-controlled peanut challenge threshold, and decreased their sensitivity to titrated skin prick testing with peanut extract. However, although all subjects reached the maintenance injection dose, most could not continue on the maintenance schedule and the rate of systemic reactions during both the rush and the maintenance phases were unacceptably high (23% and 39%, respectively). Many of the reactions involved the lower respiratory tract, causing bronchoconstriction requiring both β -agonist and injectable epinephrine treatment. Thus, further attempts to pursue this mode of treatment were largely abandoned.

2.2 Current Immunotherapy Strategies

In recent years, research in the field of food allergy treatment has had a tremendous resurgence. Multiple therapeutic strategies are currently under investigation that target IgE-mediated allergy to some of the most common food allergens, i.e. milk, egg, peanut and tree nut, rather than just treating symptoms as they occur. Two modalities have generated the most interest: oral immunotherapy (OIT) and sublingual immunotherapy (SLIT). OIT entails ingestion of a very small amount of food protein in the form of a powder or culprit food mixed with a vehicle. Protein doses are increased over 1 day in rush protocols and continued over many weeks until a maintenance dose is reached. The maintenance dose is then taken daily for months to years. SLIT typically involves food protein in the form of a liquid that is placed under the tongue for 2 minutes and then swallowed. Dose escalation and maintenance schedules are similar to those described above with OIT, and the duration of treatment can be shorter due to lower target doses associated with SLIT.

The treatment doses for OIT and SLIT differ greatly. OIT typically starts in milligram amounts and increases to several grams for a maintenance dose. SLIT usually starts with micrograms and can only be increased to milligram amounts due to the maximum concentrations of available extracts. It can be theorized that OIT could be a more effective treatment because of the higher treatment doses that can be achieved and can be easily translated to the actual food that will be ingested. However, the potential advantage to SLIT is that it may allow the food proteins to bypass gastric digestion. There are also many

tolerogenic antigen-presenting cells in the oral mucosa, which could potentially enhance the induction of tolerance, but few effector cells that are responsible for side effects.^[12]

Immunotherapy studies that have been initiated to date vary widely in study product used, starting and ending dose, study schedule, blinding, use of placebo, selection of study subjects and reporting of adverse reactions. This poses a tremendous challenge when trying to compare different treatment modalities and protocols. A recent systematic review found a general lack of uniformity in studies addressing prevalence, prevention, diagnosis, management and treatment of food allergy.^[13] Another systemic review of oral immunotherapy trials for IgE-mediated cow's milk allergy also commented on the low quality of evidence despite the existence of randomized controlled trials.^[14] In this review, we describe the relevant studies, first focusing on OIT and then on SLIT. Recently, studies have been designed to compare OIT and SLIT for milk and peanut, and these are also reviewed.

2.3 Selection of Subjects

Selecting those subjects who would be best suited for treatment is critical to the success of immunotherapy. Food allergies can be divided into two categories: IgE-mediated and non-IgE-mediated immune mechanisms. Current therapies target IgE-mediated food allergy. Additionally, children can have IgE-mediated food allergy that is transient or persistent, and the rates of outgrowing the allergy vary with the culprit food. Natural history studies show that approximately 80% of milk and 70% of egg allergic children outgrow their allergy by age 16, while only 20% of patients outgrow their peanut allergy.^[15–17] Treatment of those with transient food allergy may facilitate the acquisition of tolerance earlier than would have been achieved naturally. However, immunotherapy protocols are very demanding, with the potential of causing frequent local and, rarely, even systemic reactions. Therefore, treatment may cause more risk to subjects who would otherwise outgrow the food allergy on their own. Thus, subjects with high IgE levels and clinical history indicating a low likelihood of natural resolution may have the most to gain from immunotherapy. Conversely, these patients may be at most risk for adverse events and may be less likely to have a positive outcome from immunotherapy.

The age of the subject or timing of treatment may also be a factor. Treating a child before the allergy matures may be more successful than treating that subject in adulthood, a theory currently being tested in studies of immunotherapy for young children. In the future, targeted or individualized therapy may be necessary to address the wide variety of food allergic phenotypes.

2.4 Desensitization vs Tolerance

Many initial immunotherapy studies focused on desensitizing subjects to the culprit food by starting treatment at a very low dose and increasing the amount over time. However, by definition, desensitization is transient, meaning that the food must be eaten daily in order to avoid reactions. More recent studies have attempted to understand the induction of tolerance, which is a more permanent state of immunological change that allows for longer periods of food avoidance without reactions once the culprit food intake is re-initiated. Testing for tolerance involves discontinuation of treatment for a few weeks and then undergoing a follow-up food challenge. Table I summarizes the studies that are covered in this review. Of those that included a post-treatment withdrawal phase, approximately one-third of subjects achieved clinical tolerance to the food. Many aspects associated with tolerance induction versus desensitization still need to be elucidated, such as the optimal protocol, treatment dosing, treatment route and withdrawal period, among other factors.

3. Oral Immunotherapy (OIT)

3.1 Milk Allergy

One of the first trials using OIT to desensitize those with IgE-mediated food allergy enrolled 59 subjects aged 3–55 years (32 were younger than 16 years).^[18] A total of 29 subjects were allergic to milk; 15 to whole egg; 3 to albumin; 11 to fish; 2 to orange; and 1 each to apple, corn, beans, lettuce, peanut and peach. After initial double-blind, placebo-controlled food challenge (DBPCFC), 66 total desensitization protocols were initiated that lasted 2–3 months. Of the 54 protocols, 45 (83.3%) achieved desensitization and were able to continue to ingest the food weekly. Twelve subjects dropped out of the study due to non-compliance, and nine subjects withdrew secondary to adverse reactions with dosing. Of the 29 subjects undergoing desensitization for milk, 19 were able to complete the treatment in 3–12 months (five subjects dropped out due to noncompliance, five withdrew due to adverse reactions). A total 51.1% of patients experienced symptoms including urticaria, angioedema or abdominal pain. No difference was seen between adults and children; skin prick tests and food-specific IgE significantly decreased after 18 months, while food-specific IgG4 significantly increased after 18 months.

In 2004, Italian researchers successfully desensitized children with severe IgE-mediated cow's milk allergy.^[19] Subjects were at least 6 years old and had either a convincing history of IgE-mediated cow's milk allergy or a positive DBPCFC in this open trial. Of the 21 subjects, 15 (72%) were able to tolerate build up from a diluted drop of milk to undiluted 200 mL of milk daily over a 6-month period with only local symptoms. Three (14%) subjects were only able to tolerate 40–80 mL of undiluted milk daily and three (14%) were unable to be desensitized due to adverse lower respiratory or systemic reactions. Sensitivity on skin prick testing to casein and β -lactoglobulin significantly decreased after 6 months but milk IgE levels did not significantly change.

German researchers conducted a randomized clinical trial using OIT for cow's milk and hen's egg, in one of the first attempts to investigate the induction of tolerance.^[20] They treated 45 children, median age 2.5 years (range 0.6–12.9) with positive reactions on DBPCFC. Subjects were randomized to receive OIT to cow's milk (14 subjects), OIT to hen's egg (11 subjects), or followed as controls (20 subjects). The treated subjects underwent a median of 21 months (range 11–59) of dose build-up and maintenance treatment followed by a 2-month period of elimination. Upon re-challenge, 9 of the 25 (36%) subjects were deemed tolerant, three (12%) subjects were desensitized and needed to eat the food daily, four (16%) were partial responders who did not reach the goal maintenance dose of 8250 mg of cow's milk protein or 2800 mg of hen's egg protein, and nine (36%) subjects withdrew from the study due to reactions. Of the placebo group ($n = 20$), seven (35%) outgrew their allergy and were tolerant. Food-specific IgE decreased significantly in both the treated and the naturally tolerant control groups.

A larger randomized controlled trial was conducted in Italy and included 60 children aged 5–17 years with a positive reaction to DBPCFC. Subjects were randomized 1:1 to receive either cow's milk OIT or continue cow's milk avoidance.^[22] Subjects underwent a 10-day rush desensitization phase in the hospital, which started with a diluted drop of milk followed by an at-home build-up to 150 mL of undiluted milk over the course of 1 year and then re-challenged. Eleven (36%) subjects were able to tolerate the desensitization protocol and many were able to subsequently introduce milk products into their diet; 16 (54%) were able to tolerate 5–150 mL of milk and three (10%) were unable to be desensitized due to respiratory or gastrointestinal reactions. Almost all subjects had local reactions during both phases of treatment. Systemic reactions requiring treatment included oral steroids (8 and 17 subjects), nebulized epinephrine (18 and 6) and intramuscular epinephrine (4 and 1) during

the two phases of treatment, respectively. Of the untreated group, 6 subjects had accidental exposure to cow's milk eliciting mild reactions. Of the 30 treated subjects, 15 showed reduction in cow's milk-specific IgE at 1 year. The fact that the other 15 treated subjects had IgE above the cut-off of 100 kUA/L for reporting is the most likely reason a change was not detected in all subjects.

In the first double-blind, placebo-controlled, randomized study conducted in the US for treatment of milk allergy, 20 children aged 6–17 years with a positive reaction to DBPCFC were randomized 2:1 to receive either treatment or placebo.^[23] Of the 13 subjects, 12 (92%) were able to complete a 1-day rush dose escalation, 8-week build up and a 3- to 4-month maintenance period taking 500 mg of milk daily. Treated subjects were able to increase their milk threshold on DBPCFC from 40 mg to a median dose of 5140 mg of milk, while the tolerated threshold for placebo subjects remained unchanged. One subject withdrew from the study due to severe eczema flares. Of the total number of doses taken, 45.4% caused reactions in the treated group versus 11.2% in the placebo group. In the treated group, 35.7% of the doses caused local reactions, 18.7% gastrointestinal, 8.1% lower respiratory and 1.2% multi-system. A total of 10.2% of the doses required β -agonist and 0.2% required epinephrine treatment in the treated group. Sensitivity to end-point skin prick titration to milk did decrease significantly post-treatment. Milk-specific IgE levels did not significantly change, but there was a significant increase in milk-specific IgG4 in the treated group.

Following treatment, 15 subjects continued on an open-label protocol at home, eating measured amounts of milk-containing foods daily.^[37] Of these subjects, 13 underwent DBPCFC after a median of 17 weeks (range 13–75) post-blinded phase. Six were able to tolerate 16 000 mg of milk with no reaction, while seven tolerated 3000–16 000 mg. Of these home doses, 17% elicited oro-pharyngeal pruritus and/or localized urticaria, 3.7% gastrointestinal reactions, 0.9% respiratory, 0.8% cutaneous and 5.5% multi-system. In the initial 3 months post-treatment, 49% of doses elicited symptoms (range 2.4–96.4) while the rate decreased to 23% (range 0–79.8) in the subsequent 3 months. Therefore, reactions continued post-treatment although they decreased in frequency. Importantly, some reactions occurred with previously tolerated doses. It was also noted that reactions occurred more commonly when the doses were taken in proximity to exercise or viral illness. Milk-specific IgE did significantly decrease during this follow-up period, with milk-specific IgG4 continuing to increase.

Another Italian group conducted a single-blind, randomized, placebo-controlled study using oral immunotherapy to treat cow's milk allergic children.^[27] Subjects (n = 30, age 4–13 years) with positive DBPCFC to cow's milk were randomized 1:1 to receive either cow's milk or soymilk control. They used a weekly up dosing schedule that started with cow's milk diluted 1:25 and doubled the dose every week for 18 weeks until 200 mL of undiluted cow's milk was reached. Ten (67%) subjects were able to reach the goal dose and pass the DBPCFC compared with no change in challenge threshold in the placebo subjects. Two subjects in the active treatment group and one in the placebo group withdrew for reasons unrelated to the study and three active subjects withdrew due to reactions during treatment. Reactions experienced were mainly mild and transient, with only one subject who completed the study requiring antihistamine and corticosteroid treatment. Two of the three active treated subjects who experienced more severe reactions leading to study withdrawal required epinephrine rescue. Milk-specific IgG4 levels increased significantly in the treatment group compared with baseline.

Most recently, researchers from Spain treated children aged 24–36 months with oral immunotherapy for cow's milk allergy.^[28] Children (n = 60) with positive DBPCFC were randomized 1:1 either to receive treatment with cow's milk or to be followed on a milk

avoidance diet. Treated subjects underwent a 2-day desensitization, starting with cow's milk diluted 1:100 followed by weekly dose increases over a 16-week build-up period to a maintenance dose of 200 mL of undiluted cow's milk. After 1 year, 27 (90%) active treated subjects continued taking the maintenance dose. Of the remaining treated subjects, one continued at 35 mL of undiluted cow's milk, one withdrew due to adverse reactions, and one withdrew for reasons unrelated to the study. A total of 67% of subjects experienced cutaneous, 30% gastrointestinal, 50% respiratory and 11% associated symptoms, with two subjects requiring epinephrine once each. Regarding the avoidance group, 20 of 23 subjects had positive DBPCFC after 1 year of follow-up. In the treatment group, cow's milk-specific IgE decreased compared with baseline.

3.2 Egg Allergy

Immunotherapy protocols for egg allergy followed a similar structure to milk OIT studies. Buchanan et al.^[21] attempted to desensitize children with IgE-mediated egg allergy and further tested whether the protocol induced tolerance. They enrolled seven children, median age 4 years (range 1–7), with egg allergy for an open oral egg immunotherapy trial. Those with a history of anaphylaxis to egg were excluded. The study protocol included a 1-day modified rush desensitization starting with 0.1 mg of powdered egg white, a build-up over several weeks to 300 mg, a maintenance phase that continued for the duration of the 24-month study, followed by a DBPCFC. All seven subjects were able to escalate their doses and be challenged with 8 g of egg protein (10 g of powdered egg white); four (51%) subjects passed the challenge and continued to eat 6.7 g of egg protein in an open fashion with no symptoms. These four subjects then went on an egg avoidance diet for 3–4 months and were re-challenged. Of those four subjects, two passed the second challenge, while two failed. The remaining three subjects who underwent the first DBPCFC reacted at 2 g, 8 g and 14.7 g of egg protein, respectively. All subjects experienced mild symptoms during the rush desensitization, one subject had systemic symptoms that resolved with di-phenhydramine at build-up and no reactions occurred on maintenance. Egg white-specific IgG significantly increased from baseline, and egg white-specific IgE decreased for five subjects, although the overall mean change was not significant.

Spanish researchers used a rush protocol to desensitize children with IgE-mediated egg allergy.^[29] Subjects ($n = 23$, median age 8.1 years, range 5–17) who had a clear history of reaction after egg ingestion or had a positive oral food challenge (OFC) were included. They underwent a protocol that started with 0.001 mL of pasteurized raw egg white and increased over 5 days to 8 mL in addition to the ingestion of one whole cooked egg. They continued to ingest one cooked egg daily for 3 months, then every 48 hours for 3 months, followed by every 72 hours. A total of 20 (86.9%) subjects were able to reach the goal dose, with 14 subjects reaching it within 5 days and six subjects reaching it within 10 days. At least one adverse reaction was experienced by 18 (78.3%) subjects, with 35 mild and 20 moderate reactions to treatment doses. One subject withdrew from the study due to adverse reactions and two others continued on a slower protocol, reaching the goal dose after 60 and 80 days, respectively. Egg white-specific IgE was significantly decreased after 6 months compared with baseline, while egg white-specific IgG was increased significantly by 3 weeks.

The results of the first multi-centre, randomized, double-blind, placebo-controlled trial for the treatment of egg allergy was recently published.^[31] A total of 55 children (median age 7 years, range 5–11) were enrolled, with 40 subjects receiving OIT and 15 placebo. The OIT protocol included a 1-day dose escalation, and a build-up phase reaching a maintenance of 2 g egg white powder daily. After 10 months, 35 (87.5%) active treatment and 13 (86.7%) placebo subjects underwent OFC, and 22 (55%) active subjects passed the challenge compared with no participant from the placebo group. The subjects were followed in an open protocol, with the active treatment group continuing on maintenance therapy until a

22-month OFC. Of the 34 active participants who underwent the OFC, 30 (75%) passed and avoided all egg for 4–6 weeks; 11 out of 29 (28%) subjects then passed an OFC and whole egg open challenge. These subjects were deemed to have sustained unresponsiveness and their diets were liberalized to include egg.

Seven subjects withdrew from the study prior to reaching maintenance (two placebo – one reaction during dose escalation, one transportation issues; five active – four adverse reactions, one anxiety) and one subject withdrew from the active group due to adverse reactions prior to the 22-month OFC. Of the 11 860 doses taken by the actively treated group, 25% caused symptoms compared with 3.9% of 4018 placebo doses. Most of the symptoms experienced in the active group were oropharyngeal (15.4% of doses), while 7.8% were respiratory, 5.5% gastrointestinal, 4.4% skin and 2.2% other. No serious adverse reactions were reported that were related to therapy. Mechanistic studies revealed that egg white-specific IgG4 levels were higher for those who passed OFCs at 10, 22 and 24 months than for those who did not, and higher levels at 10 months predicted ability to pass OFCs at all three time points. Egg white-specific IgE and basophil activation levels at 10 months were lower for those who passed the 22-month OFC than for those who failed. Decreased skin prick testing wheal size at 22 months also predicted ability to pass the 24-month OFC.

3.3 Peanut Allergy

Peanut allergy has often been viewed as more serious or life threatening and only recently have treatment studies been attempted. In 2009, a UK study enrolled four subjects, aged 9–13 years with IgE-mediated peanut allergy proved by entry DBPCFC in an OIT protocol.^[24] Subjects started with 5 mg of peanut protein and increased every 2 weeks to a goal of 800 mg, which was continued for 6 more weeks at which time they were re-challenged. All four subjects increased their tolerated threshold on food challenge from 5 to 50 mg during the pre-OIT challenge to 2.38 to 2.76 g post-OIT. Symptoms occurred during dosing but were generally mild and none required injectable epinephrine.

That same year, Jones and colleagues^[25,38,39] conducted an open-label trial with OIT for 39 children aged a median 4.8 years (range 1.1–9.4) with IgE-mediated peanut allergy. All subjects underwent a 1-day dose escalation, starting with 0.1 mg of peanut protein with a goal of 50 mg. Ten (26%) subjects reached the 50 mg goal, while the remaining 29 subjects ranged from 1.5 to 25 mg. Adverse reactions involving upper and lower respiratory, cutaneous or gastrointestinal symptoms were experienced by 36 (92%) subjects during this phase. During the build-up phase, subjects increased their dose by 25 mg every 2 weeks until a maintenance dose of 300 mg was reached, which was continued for a median of 4.7 months (range 4–22). Forty-six percent of build-up doses elicited symptoms. During home dosing, 3.7% of doses caused symptoms that were mainly upper respiratory or cutaneous and 0.8% of doses caused symptoms that required treatment, including two subjects needing epinephrine injection. After the maintenance period, they underwent an OFC with 3.9 g of peanut protein; 29 subjects advanced through all three phases of the study and were challenged (ten [26%] subjects withdrew, six for personal reasons and four for persistent allergic reactions). Twenty-seven were able to tolerate all 3.9 g of the OFC with minimal side effects. These subjects continued to increase doses to a goal of 1800 mg over a total maintenance period of 36 months.

Many mechanistic markers were evaluated in the above-mentioned study. Sensitivity to titrated skin prick testing decreased significantly by 6 months. Basophil reactivity towards peanut also decreased significantly by 4 months. Peanut-specific IgE increased initially as expected and decreased to baseline levels by 12–18 months. Peanut-specific IgG4 increased significantly by 3 months and continued to increase as seen in other immunotherapy studies. *In vitro* testing of peanut-stimulated peripheral blood mononuclear cells showed an increase

in secretion of IL-10, IL-5, interferon- λ and tumour necrosis factor- α as well as initial increase in forkhead box P3 positive regulatory T cells, which eventually decreased. T-cell microarrays showed changes in many genes involved in apoptotic pathways pre-and post-OIT.

A German study enrolled 23 subjects, median age 5.6 years (range 3–14), who reacted to a median of 0.13 g (range 0.015–1) of peanut during baseline DBPCFC and underwent a rush protocol over 7 days and escalated to 0.15 g (range 0.024–3).^[26] Twenty-two subjects were able to continue with build-up, but only 14 (61%) were able to reach the maintenance dose of at least 0.5 g (range 0.5–2) after a median of 7 months (range 0–560 days). After a median of 8 weeks (range 7–13), these subjects stopped treatment for 2 weeks and then underwent repeat DBPCFC. Tolerated threshold increased at this post-treatment challenge to a median of 1 g (range 0.25–4) despite an interval gap in treatment.

Side effects were more common during the rush phase than in the build-up/maintenance phases, at 7.9% and 2.6%, respectively. Of the 6137 doses taken during build-up and maintenance, 1.3% of symptoms were lower respiratory, 0.9% gastrointestinal, 0.4% skin and 0.2% upper respiratory. No epinephrine was required in either phase of treatment. Four (18%) subjects dropped out of the study due to dose-related symptoms, including worsening of their asthma, while three (13.6%) others dropped out for factors unrelated to the study. Mechanistic analysis showed a significant decrease in IL-2, IL-4 and IL-5 produced by peripheral blood mononuclear cells post-treatment and a significant increase in peanut-specific IgG4.

Most recently, another UK study used oral immunotherapy to desensitize peanut allergic children.^[30] Subjects ($n = 22$, median age 11 years, range 4–18) with IgE-mediated peanut allergy and positive DBPCFC were enrolled. They started treatment at 0.5 mg of peanut protein in the form of peanut flour and increased every 2 weeks to a goal dose of 800 mg, which they continued to take daily for 30 weeks. Subjects underwent OFCs at 6 and 30 weeks on maintenance therapy; 19 (86.4%) subjects were able to reach the goal dose and continue onto maintenance, and 18 (81.8%) subjects were able to undergo a follow-up food challenge after 30 weeks of maintenance therapy. Challenge threshold increased from 6 mg (range 1–110) during the baseline DBPCFC to 6469 mg (800–7510). Of the 8,326 doses taken during up dosing and maintenance, gastrointestinal symptoms occurred with 6.34% of doses, oral itching/sore throat 6.2%, skin 0.77%, cough/wheeze 0.74% and rhinoconjunctivitis 0.6%. One subject withdrew due to adverse reactions during up-dosing, two subjects were only able to reach 200–400 mg, and one subject did not undergo the challenge due to inability to pass a food challenge after 6 weeks on maintenance. There was a significant reduction in peanut SPT wheal size at 6 and 30 weeks compared with baseline.

4. Sublingual Immunotherapy (SLIT)

4.1 Kiwifruit Allergy

SLIT was first studied for treatment of pollen and mite allergy in Europe. The first study using this mode of treatment for food allergy was treatment of a 29-year-old Caucasian female with severe allergy to kiwifruit.^[40] Extracts were made from fresh kiwifruit pulp and diluted. She was asked to keep the measured dose under her tongue for 1 minute and then swallowed. She built up her dose over the course of 5 weeks and reached a three times daily maintenance treatment regimen at which time she tolerated ingestion of fresh kiwi-fruit after sublingual application of the food for 1 minute. This regimen was continued daily for 5 years, at which time she had a 4-month gap in kiwifruit intake.^[41] Upon resuming kiwifruit ingestion, she tolerated it with no adverse effects.

4.2 Hazelnut Allergy

The first randomized, double-blind, placebo-controlled SLIT trial was conducted in Spain for adults with hazelnut allergy.^[32,42] Twenty-three adults were positive on initial DBPCFC and 54.5% had oral allergy symptoms to hazelnut; 12 were randomized to receive hazelnut SLIT and 11 were placebo subjects who received a saline extract. The subjects were instructed to hold the extract under the tongue for 3 minutes and then spit out. The build-up phase occurred over 4 days in an inpatient unit and 22 subjects were able to reach the maximum dose of 188.15 µg of major hazelnut allergen Cor a 1 and 121.9 ug of Cor a 8. They continued on maintenance dosing at home for 5 months and underwent a post-treatment DBPCFC. The mean threshold dose on challenge increased significantly from 2.29 g to 11.56 g in the active group compared with a change in the placebo group from 3.49 g to 4.14 g that was not significant. Of the 1466 total doses taken, three (0.2%) systemic reactions occurred, all during the buildup phase, and resolved with antihistamine treatment. Local symptoms in the form of oral itching were more common and occurred with 109 (7.4%) reactions. No change in hazelnut-specific IgE levels was noted compared with baseline but in the active group, hazelnut-specific IgG4 and IL-10 increased significantly. This study demonstrated that SLIT could effectively desensitize adults with food allergy, but since 54.5% of the subjects had oral allergy syndrome, it is difficult to apply these results more broadly.

4.3 Milk Allergy

A French group attempted to treat eight children with challenge-positive IgE-mediated cow's milk allergy in an open-label pilot study.^[33] Doses started at 0.1 mL and increased by 0.1 mL every 15 days until a dose of 1 mL/day was reached. Each dose entailed milk extract being kept under the tongue for 2 minutes and then spit out. After 6 months of treatment, seven (87.5%) subjects were re-challenged. One subject withdrew secondary to persistent oral symptoms. Milk challenge threshold significantly increased from 39 mL (range 4–106) pre-treatment to 143 mL (range 44 to 200) post-treatment. Milk-specific IgE did not significantly change during this time period.

4.4 Peach Allergy

A randomized, double-blind, placebo-controlled trial for treatment of peach allergy with SLIT was conducted in adult subjects in Spain.^[34] The 37 subjects receiving active treatment and the 19 subjects receiving placebo underwent a 5-day in-hospital build-up, followed by a three times per week maintenance dosing schedule for 6 months at 10 µg of the peach lipid transfer protein Pru p 3 per day. The doses were kept under the tongue and then swallowed. After the maintenance period, 33 (89%) active subjects and 16 (84%) placebo subjects were re-challenged. Seven subjects withdrew from the study for unrelated reasons. In the active treatment group, challenge threshold needed to elicit local symptoms was nine times higher than the threshold at the baseline challenge and three times higher for systemic symptoms, with no change in the placebo group pre- and post-treatment. Among the treatment group, 98.8% (1328/1344 reactions) of reactions were local, with 94.9% of them affecting the oropharynx; 1.2% (16/1344) of reactions were mild systemic reactions requiring antihistamine treatment. Recombinant Pru p 3-specific IgE and IgG4 significantly increased in the active treatment group.

4.5 Peanut Allergy

Most recently, interim results of another randomized, double-blind, placebo-controlled study treating children with IgE-mediated peanut allergy was published.^[35] Subjects (n = 18, median age 5.2 years, range 1.6–10.5) were randomized to receive peanut SLIT (n = 11) or placebo (n = 7). Subjects began dose escalation with 0.25 µg of peanut protein or placebo

and increased biweekly over 6 months to a maintenance dose of 2000 µg daily, which was continued for another 6 months, at which time subjects underwent re-challenge. Each dose was kept under the tongue for 2 minutes and then swallowed. Challenge results in all 11 treated subjects reached a median threshold of 1710 mg of peanut protein compared with 85 mg in the placebo group. Reactions occurred in 11.5% of active doses (480/4182 doses) and 8.6% of placebo doses (248/2875 doses). In the active treated group, 9.3% were oropharyngeal, 1.4% upper respiratory, 1.2% abdominal, 0.6% skin and 0.05% chest. No epinephrine was required for any home doses. Sensitivity to peanut titrated skin prick testing was significantly decreased in the active treatment group compared with placebo subjects. Other mechanistic studies revealed significantly decreased numbers of activated basophils after peanut stimulation, increased levels of peanut-specific IgG4, and decreased IL-5 in the active treatment group than in the placebo group.

5. Combined SLIT/OIT Studies

5.1 Milk Allergy

The first study that compared SLIT with OIT was a randomized open-label protocol that included 30 children, aged 6–17 years, with IgE-mediated allergy to cow's milk.^[36] All subjects reacted at initial DBPCFC and were treated with SLIT for a minimum of 4 weeks, starting at a low dose and increasing to 3.7 mg of milk protein. The dose was kept under the tongue for 2 minutes and then swallowed. They were then randomized equally into three groups: (i) continue to increase SLIT dose to 7 mg; (ii) cross over to treatment with OIT to 1 g (OITB); (iii) cross over to treatment with OIT to 2 g (OITA). After treatment for 12 and 60 weeks, subjects underwent OFCs and, if the post-treatment challenge was passed, they were taken off treatment, with food challenges after 1 and 6 weeks. After treatment, the challenge threshold increased significantly from baseline in all three groups: 40-fold for SLIT (ten subjects), 159-fold for OITB (nine subjects), 54-fold for OITA (nine subjects). The full challenge amount was tolerated by one subject in the SLIT group, six in OITB and eight in OITA. Subjects who passed the challenge were taken off treatment. After 1 week of milk avoidance, two subjects from the OITB group failed re-challenge. After 6 weeks off treatment, one subject from the OITB group and three from the OITA group failed re-challenge. One subject on SLIT and eight in the combined OIT group were deemed tolerant.

Adverse reactions occurred more frequently in SLIT doses (29%) than in OIT doses (23%). However, OIT doses caused more multisystem, gastrointestinal, upper and lower respiratory tract symptoms and required more β -agonist and antihistamine treatment. Injectable epinephrine was required for two subjects in the SLIT group who aspirated the dose and four subjects in the OIT groups. Two subjects withdrew due to adverse reactions during treatment (one from each OIT group).

Mechanistic studies comparing the three groups showed that sensitivity to cow's milk titrated skin prick testing decreased and cow's milk-specific IgG4 increased significantly in all groups when compared with baseline. In the combined OIT subjects, cow's milk-specific IgE and spontaneous basophil histamine release decreased compared with baseline but not in the SLIT group.

5.2 Further Research

A randomized, double-blind, placebo-controlled study is currently being conducted for treatment of children with IgE-mediated peanut allergy. In this study, 20 subjects are randomized 1:1 to receive either active OIT/placebo SLIT or placebo OIT/active SLIT.^[43]

6. Conclusion

Given the rise in prevalence of food allergy in developed countries, immunotherapy has given many patients hope for a widely available form of treatment. The studies presented in this review show that both OIT and SLIT have been able to desensitize subjects. OIT subjects, in general, have been able to reach higher challenge thresholds, become tolerant at a higher rate, and have increased changes in immunological measures, presumably due to the higher treatment doses that can be achieved, but few studies of either modality have been conducted. There is only a finite amount of liquid that can be held in the sublingual space, but it may be possible to increase SLIT doses if the allergen extracts can be further concentrated. However, the increased efficacy of OIT is offset by the higher rates of systemic reactions experienced during OIT compared with SLIT protocols. Although the rates of overall reactions are higher with SLIT, they are typically mild and isolated to the oropharynx, making the safety profile of this treatment more desirable.

Other aspects of these treatments require more research. Immunotherapy for aeroallergen sensitivity is typically continued for 3 years or more, and a longer duration of therapy may also be required for food allergens. Although most of the studies described in this review involved treatment for fewer than 3 years, a few of the recent studies are still ongoing. Combining these data with studies comparing the two modalities directly, the question of which mode of treatment will be safer but more efficacious may be answered in the next few years.

There are many questions to be answered with both modes of treatment, including subject selection, optimum dosing protocol and post-treatment management, among others. Therefore, OIT and SLIT are not currently US FDA approved or advisable for use outside the research setting. Translating food allergen immunotherapy to widespread use in outpatient offices will prove challenging. Ideally, this mode of treatment would be easily manufactured on a large scale, prescribed by the physician, dispensed and taken without error or, alternatively, given as a food product easily measured at home. SLIT is potentially more translatable for outpatient use, taking the above factors into consideration. However, caution should be used when using SLIT with liquid extracts in infants and younger age groups who may have difficulty holding the dose sublingually and present a greater risk of aspiration. Once desensitization is achieved, maintaining the food in the diet may be easier for those with cow's milk or egg allergy given the possibility of giving extensively heated forms of the culprit food.

In summary, more research is needed to conclude which mode of treatment is more effective in inducing long-term tolerance with the least amount of serious adverse reactions in those subjects with permanent IgE-mediated food allergy. However, OIT and SLIT show great promise, and a widespread treatment for food allergy may be within reach.

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Table I

Food allergy immunotherapy trials

Study, y of publication	Targeted food	Modality	Blinded	Total subjects, n (age [y])	Duration	Success rate ^a [n (%)]	Withdrawals [n (%)]	Tolerance [n (%)]
Patriarca et al., ^[18] 2003	Milk, egg, other	OIT	No	59 (3–55)	2–3 mo	45/54 (83.3)	9 (16.7)	NA
Meglio et al., ^[19] 2004	Milk	OIT	No	21 (6–10)	6 mo	15 (72)	3 (14)	NA
Staden et al., ^[20] 2007	Milk, egg	OIT	No	25 (0.6–12.9)	11–59 mo	12 (48)	9 (36)	9 (36) – off 2 mo
Buchanan et al., ^[21] 2007	Egg	OIT	No	7 (1–7)	24 mo	7 (100)	0	2 (29) – off 3–4 mo
Longo et al., ^[22] 2008	Milk	OIT	No	30 (5–17)	1 y	11 (36)	3 (10)	NA
Skiprak et al., ^[23] 2008	Milk	OIT	Yes	13 (6–17)	5–6 mo	12 (92)	1 (8)	NA
Clark et al., ^[24] 2009	Peanut	OIT	No	4 (9–13)	6–7 mo	4 (100)	0	NA
Jones et al., ^[25] 2009	Peanut	OIT	No	39 (1.1–9.4)	36 mo	29 (74)	10 (26)	NA
Blunchen et al., ^[26] 2010	Peanut	OIT	No	23 (3–14)	9 mo	14 (61)	9 (39)	NA
Pajino et al., ^[27] 2010	Milk	OIT	Yes	15 (4–13)	4–5 mo	10 (67)	5 (3.3)	NA
Martorell et al., ^[28] 2011	Milk	OIT	No	30 (2–3)	12 mo	27 (90)	2 (0.07)	NA
Garcia Rodriguez et al., ^[29] 2011	Egg	OIT	No	23 (5–17)	3 mo	20 (86.9)	1 (0.04)	NA
Anagnostou et al., ^[30] 2011	Peanut	OIT	No	22 (4–18)	2–9 mo	19 (86.4)	1 (0.05)	NA
Burks et al., ^[31] 2012	Egg	OIT	Yes	40 (5–11)	22 mo	30 (75)	6 (15)	11 (28) – off 4–6 wk
Enrique et al., ^[32] 2005	Hazelnut	SLIT	Yes	12 (19–53)	5 mo	11 (92)	1 (8)	NA
De Boissieu and Dupont, ^[33] 2006	Milk	SLIT	No	8 (6–17)	6 mo	7 (87)	1 (13)	NA
Fernandez-Rivas et al., ^[34] 2009	Peach	SLIT	Yes	37 (18–65)	6 mo	33 (89)	4 (11)	NA
Kim et al., ^[35] 2011	Peanut	SLIT	Yes	11 (1.6–10.5)	12 mo	11 (100)		NA
Keet et al., ^[36] 2012	Milk	OIT/SLIT	No	30 (6–17)	60 wk	28 (93)	2 (7)	9 (30) – off 6 wk

^aSuccess rate is defined as number of subjects who successfully finished treatment and were able to include the targeted food into the diet or finished treatment and underwent post-treatment food challenge.

NA = not applicable; OIT = oral immunotherapy; SLIT = sublingual immunotherapy.