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Oral immunotherapy for the treatment of food allergy

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Oral immunotherapy (OIT) is an emerging new therapy for food allergy. With multiple small exploratory trials and some large randomized-controlled phase 2 trials recently published and under way, there is a clear progress and interest toward making this a treatment option for patients suffering from food allergies. However, there are still many questions to be answered and parameters to fine-tune before OIT becomes an accepted option outside of the research setting. This review covers the main milestones in the development of OIT for food allergy and further discusses important specific issues that will have direct impact on its clinical application. More specifically, previous publications showing evidence for the induction of tolerance are specifically reviewed and varying safety, tolerability and efficacy parameters from previous reports are also discussed.

Allergen-specific immunotherapy (also called desensitization) is the administration of slowly increasing doses of a specifically relevant allergen for the treatment of IgE-mediated allergic diseases, until a maintenance dosage is achieved or the patient is free of symptoms.[1] Subcutaneous immunotherapy was first reported for the treatment of hay fever in 1911 by Leonhard Noon and John Freeman and the first real clinical trials were performed in the 1950s by William Frankland who showed higher doses resulted in more effective desensitization.[2] Between 1950 and 1980, allergen-specific immunotherapy was used more and more all over the world with different extracts and modalities. Interestingly, despite the widespread use of immunotherapy for over 100 y, the underlying physiology is still unclear with many proposed mechanisms.[2,3] Nevertheless, with the beginning of the food allergy epidemics at the end of the 20th century, it was only natural to attempt desensitization for this indication. (**Table 1**)

Key milestones in the development of oral immunotherapy for food allergies

The first report of food oral immunotherapy (OIT) was published in the Lancet in 1908 by AT Schofield who successfully desensitized a 13 y-old boy who was anaphylactic to egg by administering gradually increasing amounts of egg, while otherwise avoiding egg completely. The starting dose was 1/10,000 of an egg, and after six months, a challenge was negative. Thereafter he could eat an egg every day.[4] Despite this early success, literature on food OIT remained scarce for most of the 20th century, until it was "rediscovered" in the 1980s with the beginning of the food allergy epidemics.[5]

Interestingly, the first controlled immunotherapy trial for food allergy was performed through the subcutaneous route by Nelson and colleagues. The protocol involved a rush schedule over 5 d to reach maintenance of 0.5 ml of 1:100 wt/vol aqueous peanut extract, followed by weekly injections for one year.[6] All subjects undergoing subcutaneous immunotherapy had increased thresholds of reaction on oral food challenges and decreased skin prick tests compared with controls whose threshold and SPT were unchanged. However, the rates of systemic reactions and epinephrine use were found to be unacceptably high during both build-up and maintenance phases and half of the subjects required dose reductions due to systemic reactions and had subsequent complete or partial loss of protection to peanut. Considering these disappointing results, subcutaneous immunotherapy fell out of grace, which opened the way to research on alternative routes of administration which could be safer.

A lot of the early work on food OIT was performed in Europe initially outside of the research setting. Patriarca and colleagues in Italy published some of the earliest controlled studies. Using a standardized oral immunotherapy protocol for treatment of various food allergies, they reported that 83%

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Table 1. Proposed mechanisms of OIT

Proposed mechanisms of OIT
Reduced activation of basophils and mast cells
Generation of IgG4 blocking antibody
Decrease in IgE synthesis
T cell anergy
Depletion of specific Th2 Cells
Re-education of specific Th2 cells with switch to Th1 or Tr1
Induction of regulatory T cells
Induction of regulatory B cells
Induction of tolerogenic dendritic cells

of subjects could subsequently tolerate the food to which they were previously allergic. The most common food allergy in their cohort was milk, followed by egg and fish. This protocol began with a single daily oral dose of allergen that was then increased either daily or weekly until the desired final dose was reached. In comparison to age-matched food allergic controls, subjects receiving OIT demonstrated a significant decrease in food specific IgE and an increase in specific IgG4.[7] Since then, many groups have reported on their experience with food OIT with similarly high successful desensitization rates (**Table 2**).

Two large phase 2 randomized controlled trials were recently published on food OIT. Burks and colleagues published their experience with oral immunotherapy in egg allergic individuals in the USA in 2012.[23] This was a multicenter, randomized, double blind, placebo controlled study, which enrolled 55 participants, 40 randomized to egg and 15 to placebo. They included 5–18 y old subjects who had a convincing clinical history of allergy to egg and criteria for positive egg specific IgE (> 12 kU if 5 yo, > 6 kU if > 6 yo). The goal was to desensitize the subjects to 2g of egg white powder (1.6g of egg white protein). Eighteen of the 40 subjects in the egg OIT group reached 2g by 10 mo. At the 10 mo oral food challenge (OFC), 22 of the 40 (55%) subjects who received egg OIT and 0 of the 15 subjects who received placebo passed a 5g challenge. The median dose tolerated at this challenge was 5g vs. 0.05 g in the egg and placebo groups, respectively. At 22 mo there was another OFC to 10 g and 30 of 40 (75%) subjects in the egg OIT group passed the challenge. The placebo group was not required to undergo the OFC at 22 mo, unless the egg specific IgE had dropped below 2 kU, which occurred in only one subject, who did not pass this OFC. To assess for "sustained unresponsiveness," the ability to have no allergic reaction to the offending allergen after undergoing desensitization and a period of avoidance, the 30 subjects who passed the 22 mo OFC were then asked to abstain from egg for 4–6 wk and undergo another challenge to 10 g at 24 mo. Twenty-nine participants reached this endpoint and 11 (28%) subjects passed a 10 g challenge. Of the 18 participants who did not pass, 5 tolerated a dose of 7.5g, 3 a dose of 3.5g, 5 a dose of 1.5g, 4 a dose of 0.5g, and 1 a dose of 0.1g; most of the subjects had sustained a higher threshold for reaction than when they had started the protocol.

Table 2. Intention-to-treat desensitization rates in previous OIT trials

	N	Intention-to-treat desensitization rate
Milk		
Staden 2007[8]	14	64% (36% fully desensitized)
Skripac 2008[9]	13	95% (37% fully desensitized)
Zapatero 2008[10]	18	89%
Longo 2008[11]	30	90% (36% fully desensitized)
Narisety 2009[12]	15	87% (40% fully desensitized)
Pajno 2010[13]	15	73% (66% fully desensitized)
Martorell 2011[14]	30	90% fully desensitized
Keet 2011[15]	20	70% fully desensitized
Salmivesi 2012[16]	28	78% fully desensitized
Vasquez-Ortis 2013[17]	81	86% fully desensitized
Salvilahti 2014[18]	32	81%
Total	**278**	**84% [80–88]**
Egg		
Staden 2007[8]	11	64% (36% fully desensitized)
Bucchanan 2007[19]	7	57% (29% fully desensitized)
Itoh 2010[20]	6	100%
Vickery 2010[21]	8	75%
Garcia Rodriguez 2011[22]	23	96% (87% fully desensitized)
Burks 2012[23]	40	75%
Meglio 2013[24]	10	90% (80% fully desensitized)
Dello Iacono 2013[25]	10	90%
Vasquez-Ortis 2014[26]	50	82% (80% fully desensitized)
Total	**165**	**81% [75–87]**
Peanut		
Clark 2009[27]	4	100% fully desensitized
Jones 2009[28]	39	74% (69% fully desensitized)
Blumchen 2010[29]	23	78%
Varshney 2011[30]	19	84% fully desensitized
Bégin 2014[31]	40	85%
Wasserman 2014[32]	352	85%
Anagnostou 2014[33]	39	62% fully desensitized
Total	**516**	**82% [79–85]**

The immune markers studied included egg specific IgE, IgG4, skin prick test, and basophil activation. Egg-specific IgG4 antibody levels at 10 mo correlated with desensitization at 10 mo and also predicted desensitization at 22 mo and sustained unresponsiveness at 24 mo. Skin prick tests between baseline and 22 mo decreased more in the egg OIT group compared with placebo (P = 0.02). Basophil activation decreased more in the egg OIT

group compared with placebo (0.01 μg/mL, P = 0.002; 0.1 μg/mL, P = 0.001). The change in egg specific IgE from baseline to month 22 did not differ significantly in either group (P = 0.06).

This study not only showed that a longer duration of therapy led to more successful desensitization (55% at 10 mo vs 75% at 22 mo), but that sustained unresponsiveness was achievable for a small group (28%). The immune parameters studied showed changes over the course of OIT.

The other published randomized controlled study investigated peanut allergy.[33] Anagnostou et al. looked at 99 subjects, aged 7–16 y old at a single site in the UK. This was a randomized, controlled, phase 2 crossover study where subjects were randomized 1:1 to receive peanut OIT (49 subjects) vs. standard of care (50 subjects); those in the control group were then offered peanut OIT in the second phase of the study. Eligible participants had a clinical history of allergy to peanut, positive skin prick test, and double blind placebo controlled food challenge to peanut. The goal was to desensitize participants to 800 mg of peanut protein with an escalation every 2–3 wk (a total of 9 dose escalations) and to maintain 800mg/day until 26 wk. In the peanut arm, 4 participants did not reach 800mg by 26 wk during Phase 1, 5 withdrew and 1 discontinued; these 10 participants were excluded from the primary analysis. Three participants withdrew from the control arm during Phase 1. The primary endpoint was the number of participants who passed a 1400mg peanut protein double blind, placebo controlled food challenge (DBPCFC) at the end of the first phase. In Phase 1, 24 of 49 (49%, intention to treat analyses) subjects randomized to peanut OIT tolerated a DBPCFC to cumulative of 1400mg of peanut protein compared with 0 of 50 control subjects.

Both groups showed a significant improvement in the quality of life scores after treatments. There was also a small significant reduction in median peanut SPT and increase in median peanut specific IgE after OIT. There were no significant differences in basophil activation within patients after treatment, though there was a reduction in activation after treatment at the lower peanut concentrations used for activation.

The results of both trials are encouraging and many more phase 2 trials are currently underway. Nevertheless, there are many questions that still need to be answered before OIT can become standard practice (**Table 3**).

Table 3. Questions on oral immunotherapy

Eligibility	**What is the best age to do oral immunotherapy?** **Does treatment efficacy vary in different subgroup?** **Does treatment safety vary in different subgroup?**
Dosing	What is the optimal starting dose? What is the optimal maintenance dose to balance patient effort and tolerance? What is the optimal maintenance duration to achieve tolerance? How to proceed when allergic to multiple foods? What is the maximum number of foods that can be desensitized simultaneously?
Safety	How to manage dosing reactions? What is the true risk of Eosinophilic Esophagitis? Use of medication to increase desensitization speed?
Tolerance	What is the rate of tolerance? When and how should tolerance be tested? What is the goal: Desensitization vs Tolerance?
Product	Could the food be modified to be more tolerogenic? Would other routes of administration increase safety or efficacy?

Induction of clinical tolerance

While OIT has consistently been shown to induce desensitization, only a handful of trials have evaluated the efficacy of OIT to induce sustained tolerance to food allergens (**Table 4**). Desensitization is considered a temporary state in which an allergic patient becomes non-reactive to his food allergen, as long as he takes maintenance doses on a regular basis. During the desensitization period, reactivity to the allergen is expected to return if frequent dosing is discontinued. However, with prolonged treatment, long-lasting changes may occur in the immune response and some patients may have sustained unresponsiveness after stopping treatment, which is a sign of clinical tolerance.

The reported rates of clinical tolerance with food OIT has been shown to vary in previous studies. It may vary according to food, time and dose of maintenance before stopping treatment, and on the length of avoidance. **Table 4** details the current studies that have investigated tolerance after OIT. These studies are small and variable in their protocols and tolerance ranges from 13–45%. In the study by Staden et al., after 21 mo of OIT followed by 2 mo of avoidance, 36% were tolerant to serving sizes of egg or milk. This was comparable to their control group who outgrew milk and egg at a rate of 35%.[8] As mentioned previously, Burks and colleagues studied sustained unresponsiveness after 22 mo of total therapy and reported 28% rate of clinical tolerance to an 8g challenge, compared with 0% in the placebo-group.[23] Keet and colleagues looked at 3 different treatment arms with milk OIT and effects on tolerance after 60 wk of maintenance.[15] Equal numbers of subjects were allocated to sublingual immunotherapy (SLIT) alone, SLIT followed by OIT to 1g of milk, or SLIT followed by OIT to 2g of milk. Not surprisingly, rates of "tolerance" were higher in the 2g OIT group (50%), followed by the 1g OIT group (30%), followed by the SLIT group (10%), after 6 wk of avoidance, suggesting that despite the same maintenance period of 60 wk, higher doses of maintenance therapy can yield better rates of tolerance.

There are a few studies looking at peanut tolerance and here we can see how differences in maintenance doses and avoidance periods affect tolerance. Blumchen et al. studied 23 peanut allergic subjects who escalated to 500mg of peanut (roughly 2 peanuts) over the course of 9 mo.[29] After only 2 wk of avoidance, only 3 subjects (13%) were tolerant of 4g of peanut protein and these were the only 3 who were able to tolerate 1g of peanut maintenance dosing. The one subject who was able to tolerate 2g of maintenance daily was only able to tolerate 2g after 2 wk avoidance. Vickery et al. and Syed et al. both studied maintenance doses of 4000mg of peanut protein.[34] In Vickery's group, subjects

Table 4. Studies measuring the induction of sustained tolerance

Trial	Food	N	Maintenance dose	Timing of OIT	Length of avoidance	Sustained tolerance
Staden 2007[8]	Milk or Egg	25	3300 mg milk or 1600mg egg + deliberate intake	21 mo total with 7–15 mo of maintenance (median 9 mo)	2 mo	9/25 (36%) of 4770mg milk or 6200mg egg; 7/20 (35%) of control tolerant
Blumchen 2010[29]	Peanut	23	Minimum of 500mg	9 mo total with 2 mo of maintenance	2 wk	3/23 (13%) tolerated 4g; 11/23 (48%) tolerated 500mg
Keet 2012[15]	Milk	30	SLIT to 7mg SLIT + OIT to 1000mg or SLIT + OIT to 2000mg	68–90 wk of total therapy with 60 wks maintenance	1 and 6 wk	1/10 in SLIT, 4/10 in 1000mg, 8/10 in 2000mg passed 8 g challenge at 1 wk; 1 /10 in SLIT, 3/10 in 1000mg, 5/10 in 2000mg passed 8 g challenge at 6 wk at 6 wk
Burks 2012[23]	Egg	40	1600 mg egg protein	22 mo of total therapy	4–6 wk	11/40 (28%) to 8g protein
Vickery 2013[34]	Peanut	39	4000mg peanut protein	5 y of total therapy	4 wk	12/39 (31%) to 5g protein
Syed 2014[35]	Peanut	23	4000mg peanut protein	24 mo of total therapy	3 mo (27 mo) and an additional 3 mo (30 mo)	7/23 (30%) at 27 mo to 4g; 3/23 (13%) at 30 mo to 4g

underwent OIT and maintained for a total of 5 y, followed by 1 mo of avoidance, at the end of which 31% were tolerant to a 5g challenge. In comparison, the Syed cohort underwent OIT and maintenance for a total of 2 y and after avoiding for 3 mo, 30% were still tolerant to 4g. However, when these subjects then abstained for another 3 mo, roughly only half were still tolerant. The lower rates of tolerance in the peanut studies could be attributable to inadequate maintenance dose (500mg vs 4000mg) and variable OIT/maintenance periods (5 y vs 2 y).

What these tolerance tests fail to capture is that most subjects who successfully underwent desensitization still had higher thresholds for reaction on their food challenges at tolerance testing, suggesting that these subjects are still in a desensitized state. Further rigorous studies are needed to optimize protocols to achieve higher rates of tolerance.

Tolerability and impact on quality of life

When looking at the current literature on OIT, dosing reaction rates tend to vary greatly.[9,11,22,23,31,36-39] This is probably due to differences in escalation protocols, allergens, selection of participants and use of prophylactic medication. Most reported symptoms tend to be local pruritus or abdominal pain which are mostly mild and can generally be controlled with anti-histamine prophylaxis or anti-leukotriene medication.[40] This is reflected by the high rate of successful desensitization reported in those studies regardless of reaction rates.

However, severe reactions needing epinephrine injections have been consistently shown to be an occurrence, albeit rare, when performing OIT. Again, there is a great discrepancy in the indication for epinephrine in previous OIT trials. For example, Blumchen and colleagues[29] would have participants treat dose-related wheezing with albuterol, while Wasserman and colleagues would recommend epinephrine injection for episodes of isolated vomiting.[32] Interestingly, the latter group reported an important drop in their use of epinephrine after changing this recommendation to vomiting with accompanied systemic symptom without any safety issue.[41]

One valid question is whether these subjects requiring epinephrine would have had a lower frequency of severe reactions if they had continued on strict avoidance rather than undergone OIT. With peanut allergy, the annual rate of severe reactions is 1.6%.[42] In their retrospective study of 5 clinical practices performing peanut OIT in the USA, Wasserman and colleagues reported 95 uses of epinephrine in 352 patients over an average of 1.8 y (annual rate of 22%).[32] However, it must be appreciated that in the context of OIT, severe reactions are anticipated and thus recognized and treated promptly. Only 3 of the 95 reactions required a second epinephrine and none required more intensive treatment.[32] One limit to this report was that it reviewed clinical practices with different OIT protocols and that selection criteria were not reported.[43]

More importantly, it should be noted that from a patient's point-of-view, those severe reactions are generally acceptable. Food allergy is associated with a decrease in quality of life that compares to systemic lupus or type 1 diabetes, mainly due to the anxiety of potential reactions and secondary social impact.[44] The context of "expected" reactions with OIT differs from the uncertain but potential accidental reactions with avoidance. Several studies have shown a statistically and clinically significant improvement in quality of life questionnaire scores with OIT[45-47] (**Table 5**).

Table 5. Studies measuring the impact of OIT on quality of life

Trial	Number of Subjects (ages)	Intervention	QoL Change
Carraro (2012)[46]	30 (3–12 y)	Milk OIT	Improvement in emotional impact, food related anxiety, and social and dietary limitations
Factor (2012)[45]	90 (5–18 y)	Peanut OIT	Improvement in all parameters of the survey: allergen avoidance, dietary restriction, risk of accidental exposure, emotional impact, food-related anxiety, and social and dietary limitations. Parent assessment of their children 5 to 12 y old: significant improvement on all 30 questions ($P < 0.02$). Children (8 –12 y old) assessed themselves: quality of life improved on 22 of 24 questions ($P < 0.05$). Teens (13–18 y old) assessed themselves: quality of life improved on 12 of 18 questions ($P < 0.05$).
Anagostou (2014)	99 (7–16 y)	Peanut OIT	Improvement in quality of life scores assessed for 7–12 y olds by parents (median change –1·61; $P < 0·001$)
Otani (2014, under review)	40 (4–16 y)	Multiple Allergen OIT	Significant improvement in caregiver health-related quality of life (HRQL score out of 6) going from an average of 3.9 to 1.7 in 18 mo ($P < 0.0001$). All parameters in the questionnaire showed improvement. No change from baseline in control group on avoidance.

Increasing desensitization efficacy

Considering the cost and logistical burden of OIT, there is a great interest for new ways to increase desensitization speed and time to maintenance. While the use of adjuvants or modified allergens could be avenues of interest in the future, here we focus on protocols that have been reported in humans.

One approach to decrease time to maintenance that has been used frequently in Europe is rush OIT, in which the doses are rapidly increased over a few days in a hospital setting. This has been described mostly for milk and egg. In 2008, Staden and colleagues published their experience of hospitalizing 9 children in Germany, aged 3–14 y, with IgE mediated cow's milk allergy confirmed by DBPCFC.[48] The first dose was 1/100th of the eliciting dose for objective symptoms during the DBPCFC. Doses were then doubled every 2 h, with 3–5 doses during one day, with escalations up to 7 d to reach 120 mL (4g) of cow's milk or highest individual dose tolerated. Doses were reduced or repeated if subjects experienced allergic reactions. Six out of nine (67%) patients with cow's milk specific IgE ranging from 0.8 -33.8 kU/L, reached 120 mL within 3–7 d, and required 5–38 doses (median 18) to reach 120 mL. These subjects had mild side effects that did not require treatment; one subject had moderate wheezing that was treated with salbutamol. Three subjects had more reactions during the week of escalation in the hospital, one of which had a concurrent URI; these subjects did not reach 120 mL and went home on 40 mL, 6 mL, and 3 mL with plans to escalate to 120 mL as outpatients every 2–4 wk. In this small group of milk allergic subjects, they were able to show the feasibility and safety of doing an initial rush protocol in the hospital followed by home dosing. A similar approach has also been used for hen's egg allergy.[20,22]

Another approach to decrease the logistical burden of OIT has been to have subjects increase doses at home following an in-hospital rush protocol for milk allergy.[49] In this study, patients were given instructions on how to increase their doses and on how to treat specific symptoms with specific medications; notably, patients were instructed to use nebulized epinephrine followed by β-2 agonist for cough, wheeze, tightness of chest, or change in voice. Patients (132 of 140) were contacted for information about reactions at home; the number of adverse reactions were 1 for every 100 doses given. Those patients who had higher IgE (> 100 kU/L) and those sent home on low doses of milk (< 5mL) had a higher risk of reaction and higher rate of use of nebulized epinephrine.

Bégin and colleagues investigated the feasibility and safety of desensitizing multiple foods at once.[31] Thirty percent of food allergic individuals are actually allergic to multiple foods.[50-52] Compared with those with single food allergies, these participants experience a greater decrease in quality of life,[53] are more likely to suffer from dietary deficiencies,[54] and are less prone to spontaneously outgrowing their allergies.[55] If these patients undergo desensitization to each allergen one after the other, this can be very time consuming, considering protocols range from

Table 6. Oral immunotherapy trial using anti-IgE treatment

Study	Treatment	N	Age	Dose Achieved on Initial Escalation Day (mg protein)
Nadeau (2011)[60]	Omalizumab + Milk OIT	11	7–17 y	9/11 (82%) reached 1000 mg (1992mg cumulative dose)
Schneider (2013)[65]	Omalizumab + Peanut OIT	13	7–15 y	13/13 (100%) reached 500mg (992mg cumulative dose)
Bégin (2014)[39]	Omalizumab + Multiple Allergen OIT	25	4–15 y	19/25 (76%) reached 1250mg in total (2380 mg cumulative dose)

2–5 y. The protocol in the multiple food OIT study used the same schedule as peanut monotherapy but divided the dose equally between a maximum of five foods. The dose was increased up to a final maintenance dose of 4000mg of each of the food. Fifteen patients were allergic to only peanut and 25 patients had multiple food allergens, ranging from 2–5 allergens, which were included in their individual mixes. Most reactions in the multi OIT group (mOIT) were mild and comparable to single OIT with peanut. In both groups, reaction rates at up-dosing and home dosing were less than 6%. Notably, the time to reach 10 times the initial threshold dose of allergen on subsequent challenges was significantly shorter, by 14 wk, in the peanut group vs. mOIT group; the time to reach 300mg, 1000mg and 4000mg of each food allergen was also significantly shorter in the peanut only group. Overall, one can conclude that multi food OIT is as safe as monotherapy OIT, and though it may take longer to achieve the same endpoints, it is certainly shorter than sequential therapy for multiple foods.

Another approach to increase efficacy is to combine treatment with omalizumab, an anti-IgE monoclonal antibody that has been shown to increase reactivity threshold to peanut by up to 80-fold.[56] After obtaining pharmacodynamic data using basophil assays and free IgE measurements in subjects with food allergies who received standard omalizumab dosing, it was established that 8 wk post standard omalizumab therapy would be an optimal time to start oral immunotherapy.[57,58] This concept of rush immunotherapy with omalizumab was previously used in immunotherapy studies involving pollens, milk, peanut or multiple foods with promising results[39,59-65] (**Table 6**). The protocols involve injections of omalizumab based on total IgE and weight, as recommended for asthma, over 8 wk prior to and 8 wk after the start of OIT. When comparing the two phase one studies on mOIT with and without omalizumab, those in the study with omalizumab reached their final maintenance dose of 4g per allergen at a median of 16 wk compared with 85 wk in the group without omalizumab. It is also worth noting that reaction rates with home dosing did not increase with discontinuation of omalizumab after 8 wk, possibly reflecting effective desensitization.[39]

In conclusion, there are still many questions to be answered and parameters to fine-tune before OIT becomes widely accepted therapy for food allergy. With some large phase II randomized placebo-controlled studies recently published or underway, as well as multiple small exploratory trials looking at protocol variations to increase efficacy and safety, it is fair to say that the tremendous progress seen in this field is promising. However, optimizing safety and dose tolerability remain the main challenge that we currently face.

Disclosure of Potential Conflicts of Interest

The Author states he has no conflict of interest

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