Evaluating primary end points in peanut immunotherapy clinical trials

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Food immunotherapy has been the focus of several allergy research initiatives over the last decade. Although many questions remain unanswered, the evidence suggests that this treatment might be available in the near future outside clinical trials. Additionally, pharmaceutical companies, in light of promising early-stage results, have shown interest in developing commercially available products, thus increasing the likelihood that new immunotherapy treatments will be introduced, especially for peanut allergy. Given this optimistic scenario and given the prospect of rigorously developed products for peanut allergy treatment, each allergist will need to understand the specificities of these treatments and their expected efficacy and adverse event profiles. Thus it is imperative that allergists understand the differences in efficacy between the different management options, as well as how the end points are measured in the relevant literature. However, given the significant heterogeneity detected among food immunotherapy trials, this task might not be as straightforward as desired. This article aims to dissect how primary efficacy end points are defined and assessed to facilitate understanding of the design of these trials and the potential effect that this variation might have on the reported outcomes. (J Allergy Clin Immunol 2019;143:494-506.)

Key words: *Peanut allergy, food immunotherapy, desensitization, sustained unresponsiveness, randomized clinical trial, food allergy, oral food challenge*

The emerging science of allergen immunotherapy (AIT) is poised to change the landscape in the treatment of food allergy. In the very recently released European Academy of Allergy and Clinical Immunology (EAACI) food immunotherapy guidelines,[1] food immunotherapy for milk, egg, and peanut was found to be an effective intervention for increasing the threshold for reactivity. Current guidelines from US specialty societies take a more cautious approach, recommending against the use of immunotherapy, partially because of limitations in the quality of evidence.[2,3] Heterogeneity has been identified among different food AIT trials,[4] making characterization of efficacy outcomes a priority to generalize the observations of these trials.[1] Outcome homogeneity across studies is desirable to facilitate the comparison of results from different studies in a more efficient way. However, this comparability can only be achieved by using standardized definitions of efficacy measured with universally accepted tools.

Unlike other allergy fields, where standardized, validated, and risk-free assessments can be conducted to accurately appraise patients (eg, asthma control questionnaires[5-8]), in patients with food allergy, the double-blind, placebo-controlled food challenge (DBPCFC) is the only gold standard test[9] for evaluating clinical reactivity. Several efforts have been made to standardize this complicated procedure,[10-13] although individual[9] and evaluator[14] variability make this a very intricate task.

Although most of the evidence in food AIT has been gathered for milk, egg, and peanut, it is the peanut AIT model that has drawn greater attention. Peanut is one of the most frequent causes of food allergy, affecting around 1.6%[15] of the general population, and a frequent cause of anaphylaxis-related emergency department visits[16] and fatalities.[16,17] Moreover, peanut protein is a ubiquitous allergen, even present in precautionarily labeled and unlabeled products,[18] with systemic allergic reactions after exposure to small amounts and traces of peanut.[19,20]

The pharmaceutical industry has shown great interest[21-23] in developing treatment approaches for this disease, and commercial AIT products for peanut allergy might become available in

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Abbreviations used
AIT: Allergen immunotherapy
DBPCFC: Double-blind, placebo-controlled food challenge
DBRPCT: Double-blind, randomized, placebo-controlled trial
EAACI: European Academy of Allergy and Clinical Immunology
MP: Maintenance phase
OFC: Oral food challenge
OIT: Oral immunotherapy
SLIT: Sublingual immunotherapy
SU: Sustained unresponsiveness

the not too distant future. In light of the absence of normalized measurements and outcomes[1,4] and to facilitate the understanding of the subtle differences in trial designs and how these can affect reported effectiveness, the present review aims to comprehensively assess the different primary efficacy end points, examining how these end points are measured in the most relevant peanut immunotherapy trials available in the literature.

METHODS

A systematic review of the literature was performed by using the same methodology as in the meta-analysis by Nurmatov and colleagues,[24,25] although in this case the search was limited to peanut-related key words. This strategy was complemented by a manual search of the relevant databases, and every study on peanut immunotherapy was considered, regardless of the route of administration (oral immunotherapy [OIT], epicutaneous immunotherapy, sublingual immunotherapy [SLIT], or subcutaneous immunotherapy). Because the present publication aims to evaluate clinical end point definitions, as well as their advantages, disadvantages, and suitability, study designs other than controlled trials were considered, including 7 double-blind, placebo-controlled, randomized, trials[21-23,26-29]; 4 randomized trials blinded to different treatment options[30-33]; 2 randomized, unblinded controlled trials[34,35]; 2 nonrandomized controlled studies[36,37]; and 11 open-label noncontrolled studies.[38-48] Studies without an exit DBPCFC were excluded.

DEFINITION OF CLINICAL EFFICACY

There are clear similarities between conventional (aeroallergen and Hymenoptera venom) AIT and food AIT, such as the use of a dose-escalation scheme and the immunomodulation driven by the treatment. Patient safety is the main objective in both cases and also a factor that limits a broader use of the treatment.[49,50] However, although there is a robust and well-developed consensus guiding population selection in aeroallergen AIT[51] and the selection of validated clinical end points[52] for clinical trials, there remains a sizeable gap in the knowledge of food AIT, and the recommendations currently available are derived from only a few modest initiatives.[53] Indeed, the recent EAACI guidelines on the topic[1] acknowledge this gap in the evidence.

Treatment effectiveness can be defined as the ability to safely consume foods containing the culprit allergen as a result of therapy. It can be evaluated while there is continuous exposure to the offending allergen as nonreactivity either to the maintenance doses or according to the results of an exit challenge test (termed desensitization). It can also be measured after treatment has been discontinued and reassessed in a food challenge, which is most frequently referred to as sustained unresponsiveness (SU), although other terms, such as tolerance, clinical tolerance, or remission, have also been used.

Desensitization

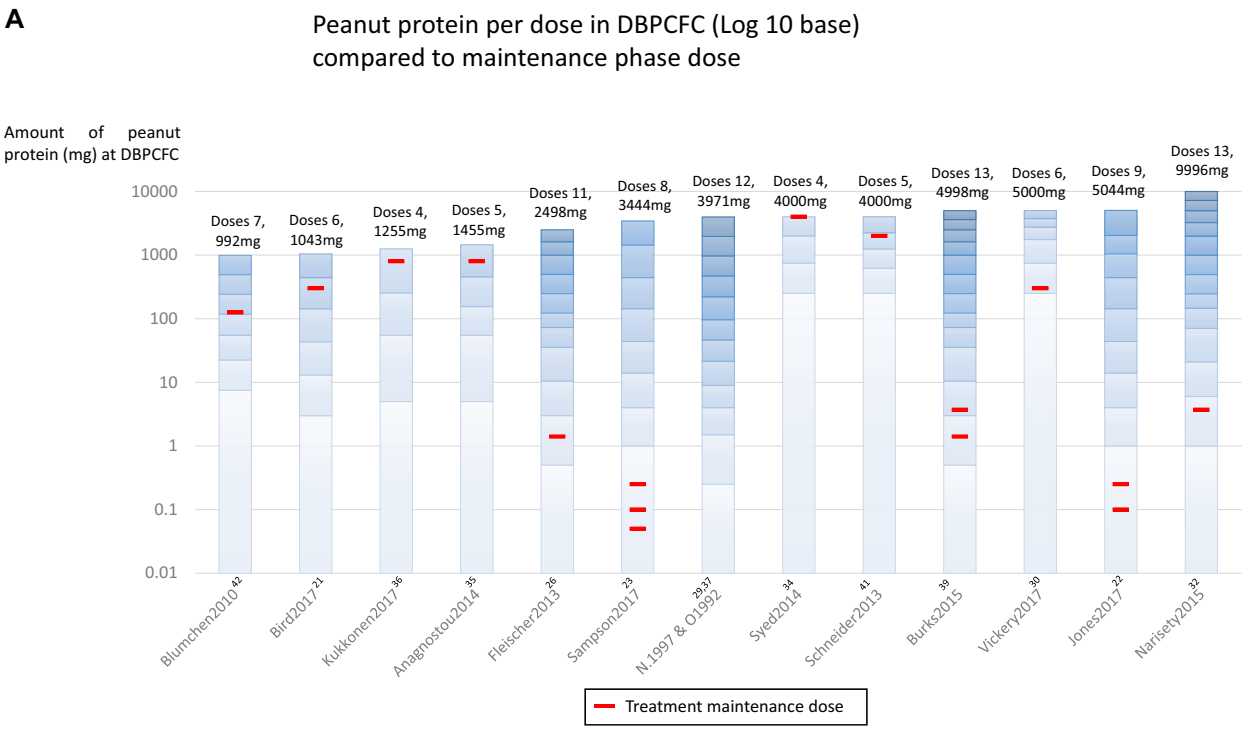
Because there is no standardized protein quantity that indicates desensitization having been achieved, studies set their own predefined amounts of peanut to be tested in an exit challenge, so that when these are tolerated, the patient is considered to have become desensitized. The total target amount varies considerably between studies (Fig 1, *A*, and Table I),[21-23,26-32,34-40,42] and the attainment of this end point is likely to be influenced by the maintenance dose itself and the length of time on maintenance, although the kinetics of desensitization are not yet well understood. Many studies historically lacked a baseline challenge in every patient,[27,28,31,40] primarily because of safety concerns, preventing the measurement of the pretreatment threshold and therefore limiting firm conclusions about the effect size of treatment; however, the inclusion of control groups[27,28,31] helps to offset some of these concerns.

Early studies on peanut AIT do not clearly state what is meant by desensitization and, rather than using predefined amounts of allergen, aim to assess statistically significant changes in subjects' reactivity thresholds to peanut in a DBPCFC. In the study by Kim et al,[28] 18 patients with peanut allergy were randomized to receive a SLIT extract of peanut or placebo. After 12 months of treatment with a maintenance phase (MP) dose targeted at 2 mg of peanut protein, the thresholds of subjects receiving active SLIT at exit DBPCFC were greater than those recorded for the placebo group (1710 vs 85 mg, $P = .011$). The study presents clear evidence of the effect of the intervention, although it is less clear whether this degree of success went beyond the statistically significant difference, irrespective of whether all patients achieved desensitization as defined in the study or whether each subject improved because patients were not challenged at entry.

Similarly, in their open-label uncontrolled study, Blumchen et al[42] investigated the efficacy of peanut OIT by comparing baseline and exit challenge thresholds and report a 4-fold threshold increase, with a median tolerated dose at exit challenge of approximately 250 mg of peanut protein. As a secondary means of measuring efficacy, they also report that 14 (61%) of 23 patients tolerated the maintenance dose of 125 mg of peanut protein. In this and a majority of other trials, desensitization is defined as a fixed amount of peanut to be eaten by the patient, thereby transforming a continuous variable into a categorical one.

There are substantial differences between the dose levels used by authors to determine desensitization. In their double-blind, randomized, placebo-controlled trial (DBRPCT), Bird et al[21] report on 55 patients with peanut allergy treated orally with a peanut extract for a median of 22 weeks and evaluated by using an exit DBPCFC, with treatment responders considered to be those tolerating a cumulative dose of 443 mg or more peanut protein.

Other trials have set larger doses, as in the DBRPCT by Tang et al,[31] which sought to assess SU in a group of 62 children with peanut allergy who received peanut OIT plus a probiotic for a median of 18.8 months. In their work the authors define desensitization as passing an exit DBPCFC at a cumulative dose of 4000 mg of peanut protein while still on therapy, with 82.1% of those receiving active treatment compared with 3.6% of placebo recipients ($P < .001$) achieving this dose.



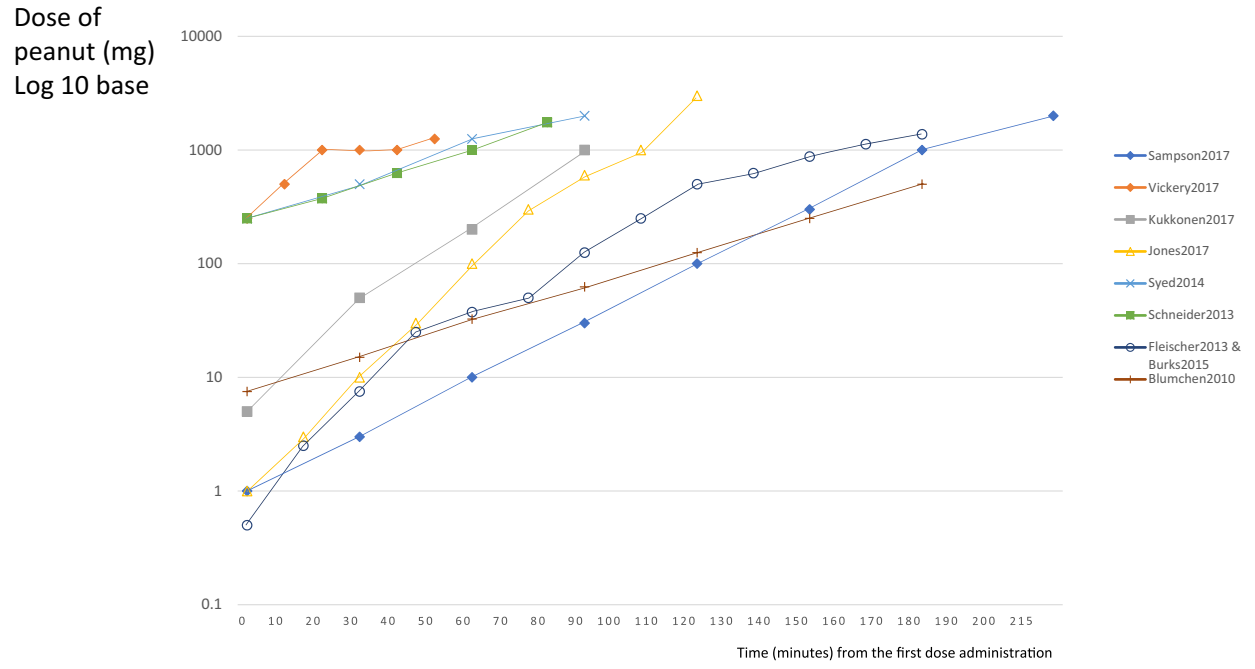


FIG 1. A, Peanut protein administered per dose (log 10 base) in exit DBPCFCs compared with MP dose. **B,** Amount of peanut protein per dose and administration over time in exit DBPCFCs. All the studies with DBPCFCs as the exit efficacy measure are included. The number of doses and total cumulative dose are summarized at the top of each column. Each study's MP dose is represented with a *red line* in all studies but those from Nelson et al[37] and Oppenheimer et al[29] because it was not provided in grams of protein. Because some studies had several active treatment arms, more than 1 line can be seen in some of them. Fig 1, *B*, represents only exit challenges that provided a detailed description on the exact amount of protein given in every dose and the interval of administration. For those studies with a range of administration (ie, Vickery et al[30] provided every dose at 10- to 20-minute intervals), the shorter interval was depicted to illustrate the fastest scenario for administering doses allowed within the challenge protocol. The studies by Fleischner et al[26] and Burks et al[39] are represented with 1 single line because the methodology is the same, with the last 2 doses given only in the study of Burks et al[39] but not in the study of Fleischner et al.[26]

TABLE I. Detailed information on food allergy immunotherapy studies in which the primary outcome is assessed through a DBPCFC

Study	Design, participants	Food AIT characteristics	Exit DBPCFC features	Primary end point
Author and year	Type of trial, no. of participants, and age	Route, dose in MP (peanut protein), full treatment duration	Single doses (peanut protein), interval between doses, stopping criteria, reported dose	Definition, efficacy results
Sampson et al, 2017[23]	DBRPCT; 221 participants; median age, 11 y (6-55 y)	EPIT, 56 placebo, 53 Viaskin (VP) 50 μg, 56 VP 100 μg, 53 VP 250 μg; 12 mo	Doses: 1, 3, 10, 30, 100, 300, 1000, and 2000 mg (total = 3444 mg) Interval: 30 minutes, repeating doses allowed Stopping: clear-cut objective symptoms, exhaustive details provided Reporting: reactive dose, last single dose eliciting symptoms	Treatment responders (eliciting dose: ≥10-fold increase and/or reaching ≥1000 mg of peanut protein in exit challenge) Responders for VP 250 μg (n = 28; 50.0%) and placebo (n = 14; 25.0%; $P = .01$); for VP 100 μg (n = 23; 41.1%), no differences vs placebo; for VP 50 μg (n = 24, 45.3%) not compared to placebo
Vickery et al, 2017[30]	Blinded, randomized to 2 treatment arms. 37 participants, median 28.5 months (9-36)	OIT, 20 patients 300 mg/d and 17 patients 3000 mg/d, median time on treatment: 29 months (25.3-47.3 months).	Doses: 250, 500, 1000, 1000, 1000, 1250 (total 4000 mg) Interval: 10 to 20 min Stopping: if clear objective evidence of allergic reaction, dose-limiting symptoms Reporting: "tolerated" cumulative dose, dose not producing dose-limiting symptoms	Subjects achieving SU (4-week elimination): ability to consume 5000 mg of peanut protein without dose-limiting symptoms during DBPCFC + 8 g peanut butter openly. 300-mg arm: 29 of 37 (78%); 3000-mg arm: 12 of 17 [71%] ($P = .43$).
Kukkonen et al, 2017*[36]	Open-label, controlled, nonrandomized; 39 participants; median, 8.3 y (6-18 y)	OIT, approximately 800 mg/d; median, 269 d (223-486 d)	Doses: 5, 50, 200, and 1000 mg (total = 1255 mg) Interval: 30 minutes; if subjective symptoms, 30 min waiting allowed Stopping: if objective symptoms emerged Reporting: "tolerated" cumulative dose	Not stringent: efficacy and long-term safety Desensitization to 800 mg: 33/39 (85%), control subjects not challenged
Jones et al, 2017[22]	DBRPCT; 74 participants; mean, 8.2 y (4-20 y)	EPIT, 25 placebo, 24 VP 100 μg, 25 VP 250 μg; 52 wk	Doses: 1, 3, 10, 30, 100, 300, 600, 1000, and 3000 mg (total = 5044 mg) Interval: 15 min Stopping: Persistent symptoms, those that required treatment or worsened Reporting: Successfully consumed cumulative dose	Treatment success, either passing the 5044-mg protein exit DBPCFC or achieving ≥10-fold from baseline to week 52 Success: Placebo, 3/25 (12%); active VP 100, 11/24 (45.8%); active VP 250, 12/25 (48%) ($P = .005$ and $P = .003$, respectively, vs placebo)
Bird et al, 2017[21]	DBRPCT; 55 participants; median active subjects, 8 y, placebo-treated subjects, 7 y (4-21 y)	OIT, 29 active subjects 300 mg/d, 26 placebo-treated subjects Median, 22 wk; IQR, 21-26 wk	Doses: 3, 10, 30, 100, 300, and 600 mg (total = 1043 mg) Interval: 20-30 min Stopping: If "dose-limiting symptoms" according to PRACTALL Reporting: "Tolerated" cumulative dose	Tolerate ≥443 mg (cumulative peanut protein) at exit DBPCFC Active subjects: 23/29 (79%), placebo-treated subjects: 5/26 (19%) ($P < .0001$)
Tang et al, 2015[31]	DBRPCT; 62 subjects; mean active, 6.1 y (± SD 2.4 y); placebo, 5.8 y (± SD 2.4 y)	OIT, 31 active 2000 mg + probiotic for 18.8 mo [IQR, 18.2-19.9 mo]; 31 placebo, no active treatment	Doses: NR (total = 4000 mg) Interval: NR Stopping: More than mild objective symptoms Reporting: Reaction-eliciting cumulative dose	SU (2-5 wk off therapy), achieved by 23/28 (82.1%) active vs 1/28 (3.6%) placebo ($P < .001$)

(Continued)

TABLE I. *(Continued)*

Study	Design, participants	Food AIT characteristics	Exit DBPCFC features	Primary end point
Author and year	Type of trial, no. of participants, and age	Route, dose in MP (peanut protein), full treatment duration	Single doses (peanut protein), interval between doses, stopping criteria, reported dose	Definition, efficacy results
Bird et al, 2015[38]	Open-label, noncontrolled; 11 subjects; median, 7 y (4-16 y)	OIT, 2000 mg/day for median of 105 d in MP and 41 wk in updosing	Doses: NR (total = 5000 mg) Interval: NR Stopping: NR Reporting: NR	Primary end point safety for treatment efficacy, not stringent: 9/11 (81.8%) tolerate 2000 mg in MP and passed the exit challenge
Narisety et al, 2015[32]	Double-blind, randomized trial; 21 participants; median, 11.1 y (7-13 y)	OIT + placebo, 11 patients receiving 2000 mg/d SLIT + placebo: 10 patients, receiving 3.7 mg/d Full treatment, 16 mo	Doses: 1, 5, 15, 50, 75, 100, 250, 500, 1000, 1250, 1750, 2250, and 2750 mg (total = 9996 mg) Interval: NR Stopping: "With clear objective signs" or "convincing subjective" Reporting: "Tolerated" cumulative dose, completing without or no more than mild symptoms	Ten-fold increase in the OFC threshold 7/10 (70%) of SLIT and 7/11 (63.6%) of OIT achieved 10-fold increase in exit vs entry DBPCFC (P = .76)
Burks et al, 2015[39] (follow-up Fleischner et al, 2013[36])	Open-label, non-controlled trial; 37 participants; median, 16 y (12-40 y)	SLIT, high-dose arm: 17 subjects, up to 3.696 mg/d, 2 y of active treatment; Low-dose arm: 20 subjects, 1.386 mg/d peanut for 3 y of treatment	Doses: 0.5, 2.5, 7.5, 25, 37.5, 50, 125, 250, 500, 625, 875, 1125, and 1375 mg (total = 5000 mg) Interval: 15-30, repeat doses allowed Stopping: Objective symptoms Reporting: Cumulative successfully consumed dose (no dose-limiting symptoms)	End of study, efficacy defined as successful consumption of 5 g of peanut protein: 2/17 (11.8%) and 2/20 (10%) in high- and low-dose groups, respectively Second definition: SU (8 wk off therapy): successfully consume 5 g of peanut protein + open feeding: 2/17 (11.8%) and 2/20 (10%) in high- and low-dose groups, respectively
Vickery et al, 2014[40] (follow-up Jones et al, 2009[47])	Open-label, nonrandomized, noncontrolled; 24 subjects, 1-16 y (follow-up Jones et al, 2009[47])	OIT, 4000 mg; mean, 1453 d (± SD 663 d)	Doses: NR, (total = 5000 mg) Interval: NR Stopping: NR Reporting: Tolerated cumulative dose	SU-4 wk: passing DBPCFC (5 g protein) + open oral feeding (eg, 8,000-10,000 mg) of peanut butter on the same day 12/24 (50%)
Syed et al, 2014[34]	Open-label, randomized controlled trial; 43 subjects; median age active subjects, 10.4 y, median age control subjects, 12 y (5-45 y)	OIT, 23 active subjects up to 4000 mg, 24 mo 20 control subjects, no intervention	Doses: 250, 500, 1250, and 2000 mg (total = 4000 mg) Interval: 30 min Stopping: Any sign of allergic reaction (ie, score≥1) on the Bock[11] Reporting: Tolerated cumulative dose	Not stringent: mechanistic study Desensitization and then SU at 3 and 6 mo of elimination diet: 20/23 (86.9%), 7/23 (30.4%), and 3/23 (13%) for each time point in active subjects. No control subjects passed the 24-mo challenge
Anagnostou et al, 2014[35]	Open-label, randomized, controlled trial; 99 subjects; median, 12.4 y (7-16 y)	OIT, 49 active subjects, 800 mg/d, 26 wk 50 control subjects, no intervention	Doses: 5, 50, 100, 300, and 1000 mg (cumulative = 1400 mg) Interval: NR Stopping: LOAEL Reporting: NOAEL	Desensitization: negative DBPCFC result (cumulative 1400 mg of protein) at exit. Active subjects, 24/39 (62%); control subjects, 0/46 (0%; P < .001)
Fleischer et al, 2013[26]	DBRPCT; 40 subjects; median, 15 y (12-37 y)	SLIT, 20 active subjects up to 1.346 mg/d, 44 wk 20 placebo-treated subjects	Doses: 0.5, 2.5, 7.5, 25, 37.5, 50, 125, 250, 500, 625, and 875 mg (total = 2500 mg) Interval: 15-30 min Stopping: Objective signs (rash; respiratory tract symptoms; abdominal pain, nausea, or vomiting; hypotension) Reporting: Successfully tolerated cumulative dose	Percentage of responders: tolerate 2500 mg or 10-fold increase on exit challenge 14/20 (70%) active subjects were responders vs only 3/20 (15%) placebo-treated subjects (P < .001)

(Continued)

TABLE I. *(Continued)*

Study	Design, participants	Food AIT characteristics	Exit DBPCFC features	Primary end point
Author and year	Type of trial, no. of participants, and age	Route, dose in MP (peanut protein), full treatment duration	Single doses (peanut protein), interval between doses, stopping criteria, reported dose	Definition, efficacy results
Varshney et al, 2011[27]	DBRPCT; 28 subjects; median, 69 mo (2.3-10.5 y)	OIT, 19 active subjects, 4000 mg/day, 12.4 mo (11.3-16.6 mo) 9 placebo-treated subjects	Doses: NR (total = 5000 mg) Interval: 10-20 min Stopping: Clinically relevant symptoms Reporting: Not clearly stated (reaction-eliciting cumulative dose?)	"Amount of peanut protein ingested at food challenge by peanut OIT and placebo-treated subjects after 1 year of treatment" Active subjects 16/19 (84%) ingested 5000 mg on exit challenge, placebo ingested median, 280 mg (range, 0-1900 mg; $P < .001$)
Kim et al, 2011[28]	DBRPCT; "18 subjects completed"; median age active subjects, 5.8 y and placebo-treated subjects, 4.7 y (1-11 y)	SLIT, 11 active subjects, 2 mg/d 7 placebo-treated subjects 12-mo duration	Doses: NR (total = 2500 mg) Interval: 20 min Stopping: If alone or in combination, appearance of "diffuse hives, severe nasal congestion, lip and tongue swelling, throat pain, coughing, moderate-to-severe abdominal pain, and vomiting" Reporting: Cumulative dose before the symptom-eliciting dose requiring treatment and discontinuation of the challenge	Evaluate the reaction threshold to peanut ingestion after 12 mo of treatment Active subjects ingested a median of 1710 mg of peanut protein vs 85 mg for placebo-treated subjects ($P = .011$)
Blumchen et al, 2010[42]*	Open-label, noncontrolled trial; 23 subjects; median, 5.6 y (3.2-14.3 y)	OIT, minimum dose in MP 125 mg, maximum 500 mg, median of 7 mo (0-560 d)	Doses: 7.5, 15, 32.5, 62.5, 125, 250, and 500 mg (total = 992.5 mg) Interval: 30 minutes Stopping: If objective clinical symptoms observed Reporting: Tolerated cumulative dose	Not stringent: Investigate the efficacy and safety of OIT 14/23 (61%) achieve 125 mg of MP dose Median 4-fold increase in the baseline vs exit DBPCFC (evaluated after 2 wk off therapy, SU)
Nelson et al, 1997[37]*	Open-label, nonrandomized, controlled trial; 12 subjects; range, 18-65 y	SCIT, 0.5 mL of 1:100 wt/vol peanut extract (not expressed in protein), up to 24 mo	Doses: 0.25, 1.25, 2.5, 5, 12.5, 25, 50, 125, 250, 500, 1000, and 2000 mg Interval: NR Stopping: "Clear-cut symptoms of a reaction" Reporting: Reaction-eliciting cumulative dose	Not stringent: Investigate efficacy and safety All exit DBPCFC results were positive. All active subjects experienced "decreased sensitivity," and the 3 subjects who tolerated maintenance remained less reactive on exit vs entry challenge.
Oppenheimer et al, 1992[29]*	DBRPCT; 11 subjects; mean, 25.4 y (14-43 y)	SCIT, 0.5 mL of 1:100 wt/vol peanut extract (not expressed in protein), approximately 35 d	Doses: 0.25, 1.25, 2.5, 5, 12.5, 25, 50, 125, 250, 500, 1000, and 2000 mg Interval: NR Stopping: When subjects had systemic symptoms Reporting: Reaction-eliciting cumulative dose	Scores in DBPCFCs and titrated SPTs Abruptly terminated for safety issues. Three active subjects finishing the study displayed a 67% to 100% decrease in symptoms, whereas 1 placebo-treated subject did not experience any change.

EPIT, Epicutaneous immunotherapy; *IQR*, interquartile range; *LOAEL*, lowest observed adverse effect level; *NOAEL*, no observed adverse effect level; *NR*, not reported; *OFC*, oral food challenge; *SCIT*, subcutaneous immunotherapy; *SPT*, skin prick test; *VP*, Viaskin Peanut patch.

*Treatment and/or challenge doses are expressed in the original article in whole peanut weight. For the shake of homogeneity of the data displayed in this table, peanut protein content was calculated considering the protein content in whole peanut, either from data provided in the main text or from others when not available.

A third and more recent way to assess desensitization is by defining an individual change in the threshold of the patient's reactivity by comparing baseline and exit challenge results, a modality of assessment more frequently seen in food AIT trials for the SLIT and epicutaneous immunotherapy routes, in which MP doses are smaller. Narisety et al[32] compared the capacity of peanut SLIT versus OIT to induce peanut desensitization, which was defined as a 10-fold increase in the oral food challenge threshold after 12 months of therapy. According to this definition, 70% (7/10) and 63.6% (7/11) of subjects initially receiving SLIT and OIT reached the target, with no differences seen between the 2 treatment modalities. However, if efficacy had been taken to be the change in baseline versus exit challenge thresholds, as in other studies, the SLIT group experienced a 22-fold increase, whereas the OIT group showed a 141-fold increase ($P = .01$), which might provide more informative data on the efficacy of both modalities than that revealed by the primary end point.

The DBRPCT by Jones et al[22] used 2 different definitions for their primary end point, either by passing a DBPCFC up to 5044 mg of peanut protein or reaching a 10-fold or greater increase in the successfully consumed dose at week 52 of treatment with a peanut-containing epicutaneous patch. Success was achieved in 3 (12%) of 25 subjects in the placebo group and 11 (45.8%) of 24 and 12 (48%) of 25 patients receiving active treatment with a dose of 100 and 250 μg, respectively ($P = .005$ and $P = .003$ placebo vs each of both active treatment arms). In terms of change in thresholds, the placebo group did not experience any posttreatment increase, whereas the increase in the tolerated dose among recipients of active therapy was 43 and 130 mg of peanut protein for the group of 100 and 250 μg, respectively ($P = .003$), which, in the words of the authors, represents a modest treatment effect.

SU

As mentioned previously, the first publication on peanut immunotherapy to introduce this efficacy parameter was that of Blumchen et al.[42] The weakness of this study is that because patients were not challenged before the 2-week off-therapy period proposed by the authors, SU could not be properly reported. Beyond this, some peanut immunotherapy studies report data on SU.[30-32,34,39,40] These all use different definitions for SU based on peanut nonreactivity, although they apply a wide range (2 weeks to 6 months) of treatment discontinuation periods. Although it is difficult to make direct comparisons across these studies because of their different methodologies and despite the few data points, there is a clear inverse correlation between time off therapy and SU when considering peanut OIT trials ($P = .036$, Fig 2).[30-32,34,40] This is exemplified in the study by Syed et al,[34] in which 20 of 23 patients with peanut allergy who passed a DBPCFC after 24 months of OIT were put on an elimination diet consisting of an initial 3-month elimination period, followed by an additional 3 months. Patients with preserved nonreactivity dramatically decreased from 20 to 7 (35%) and then to 3 (15%) at 3 and 6 months of elimination diet, respectively, thereby illustrating the transience of the treatment effect.

ASSESSMENT OF CLINICAL EFFICACY

Once clinical efficacy has been defined, researchers must state how this variable will be measured. In some cases a treatment is considered efficacious if patients reach the MP,[43,48] but usually, an exit challenge is required. Despite DBPCFC being the gold standard in food allergy diagnosis,[9] it is a cumbersome procedure. In some studies an open exit challenge has been used to evaluate patients' clinical reactivity, as well as treatment efficacy.[33,46,47] Studies in which efficacy is measured based on DBPCFC results merit a detailed characterization of the variables used.

Reported dose

When interpreting results from studies, attention should be paid to the reported dose at exit DBPCFC. In some cases the cumulative dose[29,31,37] or the single dose[23] at which symptoms occur (reactive dose) is provided. In others it is unclear whether the reported dose caused no symptoms at all or whether the dose was ingested and reported but provoked symptoms that were more than mild.[27,41]

However, it is the dose administered before the dose causing the halt of the challenge that is usually considered for analysis. We can find studies using the no observed adverse effect level,[35] which provides a clear-cut definition (ie, the dose administered before any adverse effect occurs during the challenge). In other cases different terminology has been created to indistinctly refer to doses not causing symptoms or merely inducing mild transient problems. Either tolerated doses[21,30,32,40] or successfully consumed doses[22,26,39] are included under this last category despite their subtle differences in meaning, which are only perceivable after close interpretation of the challenge-stopping criteria.

Challenge-stopping criteria

When diagnosing food allergy, challenges classify patients as allergic or nonallergic. However, in food immunotherapy research settings selecting the stopping criteria is a delicate matter because this parameter can affect the effect size of the intervention. According to current guidelines,[9,14] parameters for stopping and declaring a challenge result as positive should be clearly specified beforehand and reported. In some cases stopping criteria are not published[27,38,40,46,47] or are explained with insufficient depth.[27,36,45] However, studies that do provide more information either refer the reader to published DBPCFC consensus,[21,34,35,41] provide a nonexhaustive list of symptoms leading to challenge discontinuation,[26,28-32,37,39,42] or both.[22] One exception is the publication by Sampson et al,[23] in which the full protocol is available. In general, the positivity criteria leave some room for uncertainty as to whether the patient fully tolerated the reported dose or had only mild symptoms at the time. Although these mild symptoms might not be grounds for suspending the challenge because they can also be present in negative food challenge results and with placebo feedings,[54] they might mark the onset of what will be a full-blown allergic reaction with more gradual development, thus causing positivity to be wrongly attributed to the subsequent dose or doses.

In all but 2 studies,[32,45] subjective symptoms are either not considered as stopping criteria or there is no clarification as to how subjective symptoms were handled in the challenges. Although objective symptoms are recommended for discontinuing challenges,[9] in the highly relevant study of EuroPrevall on food allergy prevalence, a challenge was also considered positive if severe and/or persistent (lasting >45 minutes) subjective symptoms[55] appeared. Subjective

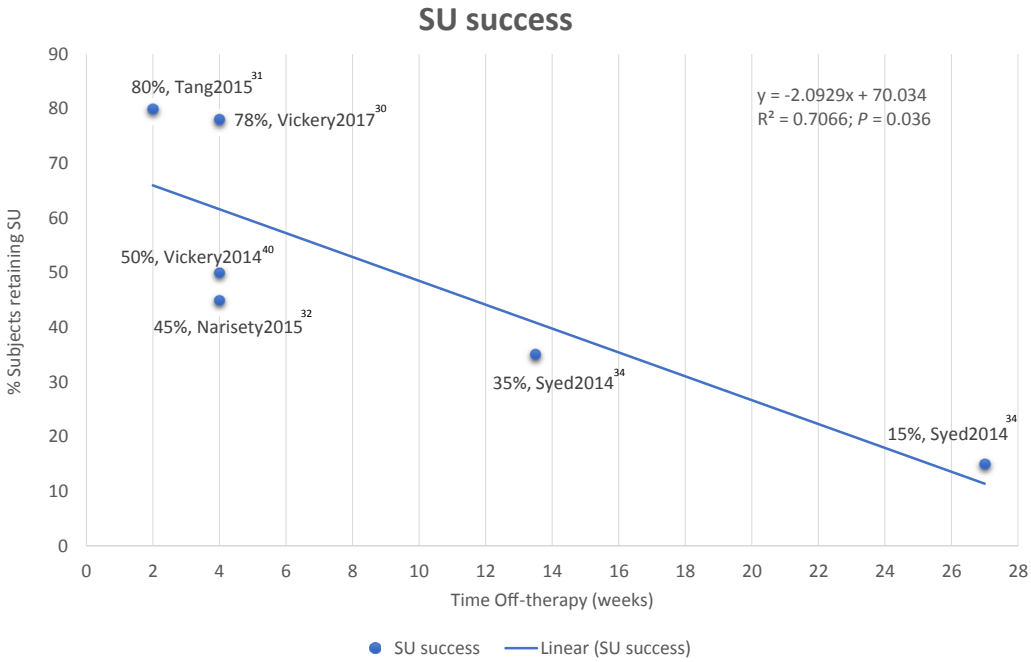


FIG 2. Relationship between SU and time off therapy. Despite difficulties in making comparisons and considering only the off therapy time in the different peanut OIT studies reporting on SU, a decrease in SU is observed with longer off immunotherapy periods. For studies reporting time off therapy in months, the equivalence of 1 month = 4.5 weeks was used.

symptoms have been shown to precede objective symptoms,[19] which again might be a confounding factor when reporting the dose to which a positive challenge is accredited (Fig 3).[21-23,26,29-32,34-37,39,56]

Challenge schedules

Cumulative doses at exit challenge vary greatly across studies (Table I). Greater doses are usually used in trials in which the MP is performed with larger amounts of peanut. Schneider et al[41] use a cumulative dose of 4000 mg of peanut protein in an exit challenge carried out in subjects receiving 2000 mg of peanut protein during MP. On the other hand, lower cumulative doses are seen in studies with lower MP doses, as in the study by Anagnostou et al,[35] whose patients received 800 mg of peanut protein in MP, and the cumulative dose at exit challenge was 1400 mg. Despite this pattern, there are some exceptions to this rule.[22,23,26,39]

Among studies with an exit DBPCFC in which detailed information is provided on the amount of protein administered in each dose, larger increments occur in the initial doses, with 10-fold increases seen in some studies[35,36] and more conservative increments of 2- or 3-fold in the last doses (Fig 1, *A*).[22,38] Also, fewer steps are usually needed to achieve the cumulative dose in food challenges when the maintenance dose is similar to that given in the challenge.[34,36] To the contrary, with a more cautious approach, more doses are given in studies with lower treatment doses in MP and/or when there is an untreated population, which will also be challenged but will not be protected by the intervention (Fig 1, *A*).[26,29,32]

The last relevant factor concerning challenge schedules involves the time interval between administered doses. Again, we found that these data are not reported consistently, ranging from 10 to 30 minutes. Considering extreme values for interval range, the shortest of the challenges among the reviewed studies could be completed in 50 minutes,[30] whereas in the longest, the last dose could not have been administered until 330 minutes after the challenge was started (Fig 1, *B*).[26] Because food challenges are not a straightforward procedure, if mild and doubtful symptoms arise, it is recommended to postpone the next dose to allow the reaction to run its course.[9,14] Nonetheless, it is remarkable that only 2 studies[23,36] describe the prospect of dose postponement, and in the remaining trials under review, this issue is not mentioned at all.

Extract for challenges

Peanut is a highly complex allergenic source, and processing of peanut can modify its allergenic profile. High-temperature roasting increases its allergenicity[57] by creating neo-epitopes in a Maillard reaction, and boiling reduces its IgE-binding capacity.[58] The diverse allergens and their quantity contained in peanut AIT extracts are not usually specified, and it has recently been proved[59] that significant differences do exist. Additionally, there is no clear indication of which extract is used in exit challenges, although in most cases the product used for food AIT is also used in the challenge.[29,35,37,41,42] Where this is the case, maximum efficacy is expected because the specific allergenic repertoire protection conferred by treatment perfectly matches the allergen profile in the culprit extract, and thus it is unknown how the patient might react to different peanut foodstuffs given the considerable differences among peanut products.[59] Alternatively, some studies use different extracts,[22,26] whereas in other cases, after the exit DBPCFC has been completed, an open challenge is conducted with a different common peanut product,[40,45] providing information on the extent

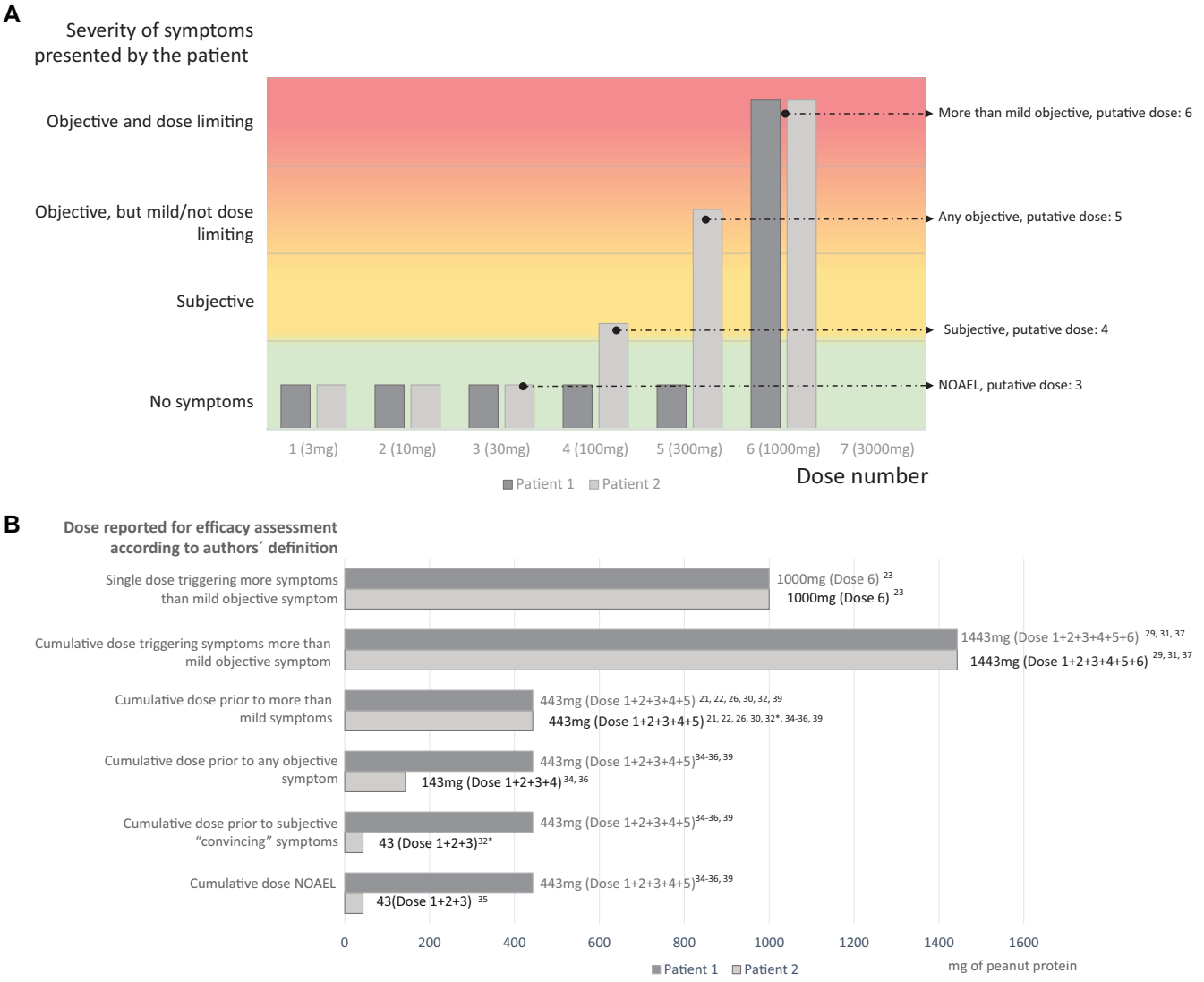


FIG 3. A, Stopping criteria and putative dose. For illustrative purposes, a hypothetical challenge with the recommended doses in PRACTALL was used. This figure represents 2 possible symptom evolutions in DBPCFCs, according to the previously described phenotypes of response in peanut challenges.[56] Patient 1 depicts a patient without any symptoms until dose 6 is administered and then rapid onset of objective symptoms leading to challenge discontinuation. Patient 2 presents with slow evolution through different degrees of clinical manifestation from subjective to more than mild objective symptoms in the last stage. **B,** Effect of dose reported in the size of the effect. In Fig 3, *B*, both patients' challenge results have been interpreted, and the reported dose according to each protocol is depicted. For patient 1, the reported dose to assess efficacy might vary from 443 to 1443 mg if the cumulative previous dose or the cumulative dose triggering symptoms is considered, respectively. In patient 2 the differences are more striking, from 43 mg if the no observed adverse effect level dose is considered to 1443 if the cumulative dose triggering symptoms is selected for the primary outcome assessment. *The stopping criteria in Narisety et al[32] include both more than mild symptoms OR subjective convincing symptoms, so if the subjective symptoms were "convincing" the dose could have been 1+2+3, whereas if just "nonconvincing," this would have been dose 1+2+3+4+5.

to which the treatment was also efficacious for other peanut foodstuffs.

Another factor adding complexity to the selection of the challenge extract is the interaction between the vehicle matrix and the peanut proteins. Information regarding matrices is scarce among the articles reviewed, although it is acknowledged that matrix and fat[60,61] content can modify allergen-epitope expression. Therefore future attempts at standardizing outcomes in food immunotherapy trials might need to address this point.

DISCUSSION

This is a momentous period in the history of food AIT, despite several unanswered questions[62] and an ongoing debate on whether this management approach is ready for routine clinical practice.[63-69] The most recent EAACI guidelines marked a step toward widespread introduction of immunotherapy, signaling that it could soon be suitable for everyday care delivery[1] in specialized centers. Now is the time to build up a solid evidence base, designing harmonized studies for the most crucial variables.

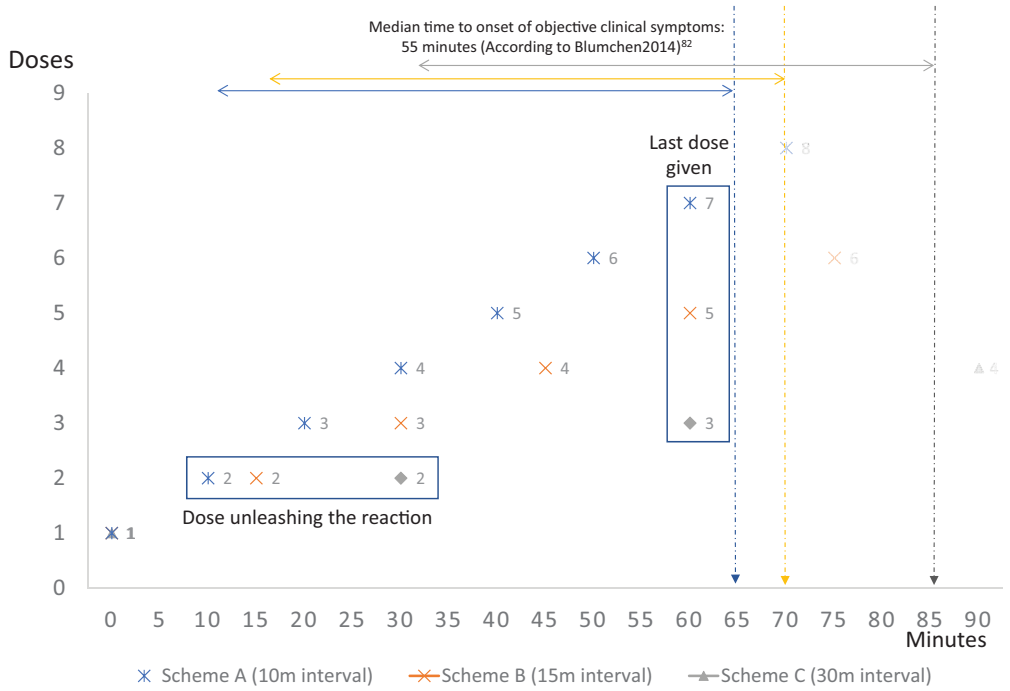


FIG 4. Relationship between doses and administration intervals. The hypothetical scenario depicted in this figure represents 3 different challenge schemes (A, B, and C), where doses are scheduled to be given every 10, 15, and 30 minutes. Considering that the reaction is always unleashed by dose number 2, and assigning a 55-minute interval (according to previously data published by Blumchen et al, 2014) until the reaction is clinically acknowledged, it is illustrated how protocols with shorter intervals favor larger right censoring of the information.

By doing this, different studies can be compiled and subjected to meta-analyses, thereby minimizing heterogeneity, a recurring handicap of evidence on other forms of immunotherapy derived from pooled data.[50]

In AIT, clinically meaningful differences in primary outcome have been established as a 15% or greater to 20% or greater change in active therapy relative to placebo.[70] Nowadays, there is no consensus within food AIT on what qualifies as clinically meaningful results. In randomized controlled trials desensitization efficacy has been defined in terms of statistical differences in thresholds between active treatment and placebo/control groups[27-29] at exit challenge, as well as by nonreactivity to an arbitrary fixed amount of peanut[21-23,26,30,31,35] and/or by increasing each subject's thresholds an arbitrary number of times.[22,23,26,32] It is known from studies of precautionary labeling that low amounts of peanut protein can trigger allergic reactions.[71] Deschildre et al[72] reported that among the 238 patients for whom the eliciting dose could be calculated after real-life reactions, in 44.3% the triggering dose was less than 100 mg of peanut protein. Baumert et al[73] combined data on individual reactivity thresholds and peanut contamination levels in different food products and computationally estimated that changing a patient's threshold from 100 mg or less of peanut protein to 300 mg reduces the risk of accidental reaction by more than 95%.

Still, reactions to nonlabeled foodstuffs do occur, even in supposedly safe environments,[74] as do reactions to larger allergen doses. Additionally, larger doses can pose a greater risk of more severe reactions,[75] and therefore designing treatments that protect against larger doses is recommendable. However, how large these doses should be is a question that remains unanswered.

These considerations on reactions to low doses have been the motivation behind studies aiming for lower desensitization levels. The ultimate end of this research is to protect allergic patients against accidental exposure, and strict avoidance of peanut is advised regardless of the treatment.[21] On the other hand, in studies with higher desensitization thresholds, patients are allowed to normalize their diets and consume peanut *ad libitum*.[32,40]

Given that postdiscontinuation efficacy seems to be transient and having abandoned the overly optimistic terms tolerance and even cure,[62] this assessment is nonetheless highly relevant as an efficacy end point. Because several variables, such as therapy duration and dose, patient profile, adherence, and others,[76] are crucial to this outcome, the period of treatment discontinuation is the only indicator of what this assessment actually represents. Again, uniform off-therapy periods are desirable to pool data from different studies to better understand this variable.

DBPCFCs are recommended by academies of medicine[1] and regulatory bodies[53,77] to measure primary efficacy outcomes in food AIT, but it is unlikely that these results mirror the real-life patient response,[78] mostly because of described cofactors that modify a patient's threshold, such as exercise, infection, menses, and others.[79,80] Even within the tightly controlled scenario of a DBPCFC, individual response varies greatly, as demonstrated by Glaumann et al.[81] In their study of children with peanut allergy, a peanut DBPCFC was followed by a single-blind challenge within 1 month. Of the 14 children with a positive DBPCFC

result, only 2 reacted in the single-blind challenge at the same threshold and with the same severity score.

We have seen how ignoring subjective symptoms can have a negative influence on the accuracy with which reaction-causing dose levels are selected. Proper threshold selection can be further precluded by shorter dose intervals, especially if we bear in mind that using a modified peanut challenge protocol with 2 hours between doses, Blumchen et al[82] described a median latency of clinical reaction (objective clinical symptoms) of 55 minutes (range, 5–210 minutes). The effect of this delay is difficult to estimate; however, a few hypothetical scenarios have been recreated in Fig 4 for the purposes of illustration.

Because the doses triggering allergic reactions are a continuous variable that varies from subject to subject and considering that food challenges can only report information from discrete doses, the true results of our intervention are only partially known or are "censored." If challenges were stopped at the presentation of subjective symptoms, our information would be "right censored" because the final (true) result might be greater than the observed result.[9] On the other hand, using shorter administration intervals, reporting reactive dose, ignoring subjective and/or mild objective symptoms, using challenge schemes with fewer doses, or not prolonging the waiting period before the next dose administration in case of doubtful reactions might lead to left censoring, potentially causing overestimation of the real efficacy of our treatment. Unfortunately, until validated alternatives are developed, the field is left with discontinuous exit food challenges that must be done in graded fashion for safety reasons, especially when control groups are used. Single-dose challenges have been used to validate eliciting doses in children with peanut allergy[83] and could be considered after or as an alternative to DBPCFCs to demonstrate clinically meaningful protection while addressing the limitations of graded dosing, as has been previously used in some peanut AIT trials.[30,40,45]

One final concern about the real-life efficacy of food immunotherapy stems from the partial (threshold-limited) protection provided by these therapies. It is a clinical observation but has also been suggested previously[19] that mild and/or subjective symptoms represent a warning sign that a patient has consumed a contaminated foodstuff, after which the patient immediately discontinues intake. If with AIT those early signs and symptoms disappear or only appear with a higher allergen intake, then theoretically, an accidental exposure might not be as readily detected. Whether this would lead to reactions of similar severity caused by larger exposures or to more severe breakthrough symptoms has yet to be established. Clinical field efficacy trials measuring the rate and/or severity of reactions to accidental food exposures outside controlled challenges might provide us with answers to this question.[53,77]

In conclusion and despite the high internal consistency of well-designed DBRPCTs recognized here, there is a lack of harmonization between some crucial variables, which can hamper efforts to pool the results of these studies and thus hinder the further application of this treatment. The authors call for a coordinated and sustained international effort that includes perspectives from all stakeholders, including patients, health care providers, industry, government, insurers, and regulators, with the goal of creating a common framework for food immunotherapy study design. Such an effort will help to ensure that today's research findings can be clearly understood and compared, leading to valuable and meaningful future treatments.

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