Adv Ther (2021) 38:4321–4332
https://doi.org/10.1007/s12325-021-01843-2

ORIGINAL RESEARCH

The Risk Reduction of Accidental Exposure-Related Systemic Allergic Reactions Extrapolated Based on Food Challenge Data After 1 Year of Peanut Oral Immunotherapy

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Received: April 21, 2021 / Accepted: June 23, 2021 / Published online: July 8, 2021

ABSTRACT

Introduction: The phase 3 trial PALISADE, comparing peanut (*Arachis hypogaea*) allergen powder-dnfp (PTAH) oral immunotherapy versus placebo in peanut-allergic children, reported that a significantly higher percentage of PTAH-treated participants tolerated higher doses of peanut protein after 1 year of treatment. This study used PALISADE data to estimate the reduction in the risk of systemic allergic reaction (SAR) after accidental exposure following 1 year of PTAH treatment.

Methods: Participants (aged 4–17 years) enrolled in PALISADE were included. Parametric interval-censoring survival analysis with the maximum likelihood estimation was used to construct a real-world distribution of peanut protein exposure using lifetime SAR history and highest tolerated dose (HTD) from a double-blind, placebo-controlled food challenge conducted at baseline. The SAR risk reduction was extrapolated using the exposure distribution and the HTD were collected at baseline and trial exit for PTAH- and placebo-treated participants.

Results: Assuming a maximum peanut protein intake of 1500 mg, participants were estimated to have $< 1\%$ probability of ingesting > 0.01 mg during daily life. The mean annual SAR risk at trial entry was 9.25–9.98%. At trial exit, the relative SAR risk reduction following accidental exposure was 94.9% for PTAH versus 6.4% for placebo. For PTAH-treated participants with exit HTD of 600 or 1000 mg without dose-limiting symptoms, the SAR risk reduction increased to 97.2%. The result was consistent in the sensitivity analysis across different parametric distributions.

Conclusion: Oral immunotherapy with PTAH is expected to result in a substantially greater reduction in risk of SAR following accidental exposure compared to placebo among children with peanut allergy.

Keywords: Accidental exposure; Immunotherapy; Peanut allergy; peanut (Arachis hypogaea) allergen powder-dnfp; Systemic allergic reaction risk reduction

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-021-01843-2.

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Key Summary Points

Why carry out this study?

Peanut (*Arachis hypogaea*) allergen powder-dnfp (PTAH) is approved in the United States for peanut-allergic individuals aged 4-17 years to mitigate allergic reactions due to accidental allergen exposure.

The PALISADE trial demonstrated that PTAH oral immunotherapy effectively increases the tolerated threshold of peanut protein in allergic patients during a double-blind placebo-controlled food challenge.

This study used clinical trial data from PALISADE to estimate the distribution of accidental peanut protein exposure and to extrapolate the reduction in risk of systemic allergic reaction associated with 1 year of treatment with PTAH versus placebo.

What was learned from this study?

Using data from PALISADE, this study estimated that treatment with PTAH for 1 year resulted in a ~95% reduction in the risk of systemic allergic reaction due to accidental peanut protein exposure during daily life among children (aged 4-17) with peanut allergy.

The estimated ability of PTAH to substantially reduce risk of systemic allergic reaction due to accidental peanut protein exposure can help inform the treatment decisions of peanut-allergic patients.

INTRODUCTION

Peanut allergy is the most common cause of food allergy among children and adolescents [1–3]. Although the elicited allergic reactions are rarely life-threatening, peanut allergy still accounts for the majority of food allergy-related fatalities [4, 5]. The prevalence of peanut allergy among children continues to increase in the United States (US) and Europe [2, 6].

The substantial burden of illness related to peanut allergy results in high health resource utilization and associated medical costs, as well as a negative impact on patients' quality of life [7, 8]. A 2013 US-based survey study calculated a US$24.8 billion annual cost with $4.3 billion due to direct medical costs related to pediatric food allergy, or $4,184 per child/year [9]. In that study, hospitalizations accounted for $1.9 billion, followed by allergist ($819 million), emergency department ($764 million), and pediatrician ($543 million) visits. Between 3 and 55% of peanut-allergic individuals experienced at least one unexpected allergic reaction in a 1-year period [10], and, although it is rare, peanut allergy is the leading cause of food allergy-related death in children [11, 12].

Peanut allergy is difficult to manage effectively due to its complex etiology and variation in possible risk factors [13]. Until recently, there were no treatments approved in the US, and, therefore, the primary approach has been avoidance of peanut-containing foods and the use of rescue medicines (i.e., epinephrine and antihistamines) in the event of exposure [13, 14]. However, people may ignore or misunderstand the label listed on packaged food, resulting in the accidental consumption of peanut protein. Furthermore, because unpackaged food does not need to be labeled for the presence of peanut protein, accidental exposure via this route may be much more common. Restaurant-prepared food and meals prepared at home or social events, where patients and caregivers may not realize the existence of peanut protein, can prompt an unexpected allergic reaction with varying levels of severity [15, 16].

This unmet need has prompted investigations into novel immunotherapy as potential treatments for peanut allergy [17], one of which is the peanut-derived oral biologic immunotherapy peanut (*Arachis hypogaea*) allergen powder-dnfp (PTAH). In January 2020, PTAH, formerly known as AR101, became the first-in-class standardized oral immunotherapy

approved by the US Food and Drug Administration (FDA) to mitigate allergic reactions that may occur with accidental exposure to peanuts in individuals 4–17 years of age with a confirmed diagnosis of peanut allergy [18]. PTAH delivers a daily maintenance dose of 300 mg of peanut protein with a characterized and consistent component allergen profile, following the Initial Dose Escalation phase and the Up-Dosing phase. The phase 3 trial PALISADE examined the outcomes of patients with peanut allergy in a double-blind placebo-controlled food challenge (DBPCFC) after receiving PTAH or placebo for 12 months (6 months Up-dosing followed by 6 months Maintenance) [19]. The trial reported that, at the exit food challenge, 67.2% of PTAH-treated patients but just 4% of the placebo patients were able to ingest a dose of ≥ 600 mg peanut protein (approximately two peanuts) without dose-limiting symptoms. Moreover, the median highest tolerated dose (HTD; the maximum dose with no more than mild symptoms) for PTAH-treated patients increased 100-fold, from 10 mg (equivalent to 1/30th of a peanut) before treatment to 1000 mg (three or four peanuts) after 12 months of treatment.

To provide a standard efficacy measurement in food allergy studies, in 2016, the FDA Allergenic Products Advisory Committee recommended the DBPCFC based on its relevance in replicating the associated allergic reactions to an accidental food allergen exposure [20]. While the DBPCFC used in PALISADE provides a measure of PTAH's treatment effect, healthcare decision-makers assessing a therapy's benefits are also interested in understanding the associated risk reduction. For example, it would be clinically meaningful and easy for patients and caregivers to understand that the percentage of risk reduction for the PTAH group was 90%, when those patients who originally could tolerate no more than 10 mg of peanut protein before treatment could now tolerate 1000 mg. To quantify the risk reduction associated with PTAH, information on patients' accidental exposure to peanut protein is needed, but real-world exposure patterns are not well documented or categorized. An observational multicenter survey study assessed the peanut protein exposure among patients in Europe but the results reflected country-specific, highly variable consumption patterns [21]. Moreover, data were only collected for patients who were experiencing an allergic reaction at that time, with an estimated median eliciting dose of 125 mg (interquartile range: 34–177 mg), which does not represent their very low routine peanut protein intake while practicing avoidance. Although challenging, there has also been research to measure the amount of peanut protein from a variety of packaged foods [22, 23]. However, peanut protein intake from non-packaged foods cannot be accurately quantified.

To provide a quantifiable perspective of accidental peanut protein exposure patterns during daily life, this study used clinical trial data from PALISADE to estimate the distribution of accidental peanut protein exposure. Based on the estimated distribution, the risk of systemic allergic reaction (SAR) and the risk reduction associated with 1 year of treatment with PTAH compared with placebo were calculated using patients' HTD measured via the DBPCFC during PALISADE.

METHODS

Data Source

The PALISADE study was a double-blind, placebo-controlled phase 3 trial which enrolled peanut-allergic patients aged 4–55 years [19]. At screening, all patients underwent DBPCFC, and those with dose-limiting symptoms at or before a challenge dose of 100 mg of peanut protein were eligible. Patients were randomly assigned in a 3:1 ratio to receive PTAH or placebo. After completing the regimen, participants underwent a DBPCFC at trial exit in a similar fashion to the screening food challenge. The total duration of the trial was approximately 12 months. Consistent with the primary analysis population in PALISADE, this study included patients aged 4–17 years, with 372 receiving PTAH and 124 receiving placebo.

Statistical Analysis

A two-stage analysis was considered to assess the SAR risk, in which the peanut protein exposure distribution was estimated in the first stage and the risk reduction was evaluated based on the estimated distribution in the second stage. The analysis focused on SAR risk associated with accidental exposure and did not examine iatrogenic reactions, as these have been examined elsewhere [19].

Stage 1: Estimation of Peanut Protein Exposure Distribution Using PALISADE Baseline Data

Baseline data collected in PALISADE were used to estimate peanut protein exposure. This included patients' prior histories of SAR and patients' HTD collected via the DBPCFC conducted at screening.

The daily risk of SAR was defined as the probability of having a SAR in 1 day. In order to assess the risk of SAR, two inputs are needed: a patient's daily accidental exposure to peanut protein and their HTD. A parametric distribution was assumed for the former. The maximum value for the daily accidental exposure was assumed considering that patients with peanut allergy would attempt to avoid consuming food high in peanut protein, and that accidental exposure is usually due to a limited amount of peanut. The value of 1500 mg (approximately five to six peanut kernels) was considered in the primary analysis and 2000 mg (approximately 8 peanut kernels) was considered in the sensitivity analysis [24]. During the DBPCFC at screening in PALISADE, the minimal eliciting dose (MED; the lowest dose triggering allergic or systemic allergic reaction) was estimated for all patients from their HTD as one dosage level higher as administered in the DBPCFC, e.g., a patient's MED would be set to 10 mg if their prior dose of 3 mg was determined to be the HTD. When peanut protein intake for a patient was equal to or exceeded their MED, then a patient would be assumed to have a SAR. These thresholds were used to understand the threshold over which a SAR was expected to occur. In addition, baseline questionnaire data on the number of prior SARs over each patient's lifetime were used to estimate the likelihood of accidental exposure. Accidental exposure was assumed to follow a binomial distribution based on the timeframe (i.e., a patient's age in days) during which prior SARs occurred and their daily SAR risk [25]. The maximum likelihood approach was used to estimate the daily accidental peanut protein exposure based on Weibull, log-normal, and log-logistic distributions using PALISADE baseline data of HTD and prior history of SAR. This method is equivalent to an interval-censoring survival analysis that was used in previous peanut threshold research [25–27]. More details are provided in the Supplementary Material.

Stage 2: Calculation of Relative Risk Reduction

Based on the estimated peanut protein exposure distribution in Stage 1 and HTD, the daily absolute risk of SAR was calculated and further converted to the risk over a 1-year period (Supplementary Material), as the latter was a common measure reported in the literature [28]. The risk reduction associated with treatment was defined as the risk difference of SAR before the treatment (i.e., baseline) and after the treatment (i.e., trial exit). During DBPCFC at trial exit, patients' HTD was measured and the same algorithm was used to estimate their MED value. However, about half of the patients did not experience dose-limiting symptoms at 1000 mg and no higher dose was administered in the food challenge per trial protocol. With the consideration of maintaining a sufficient sample size for the analysis, the MED of these patients was conservatively assumed to be 1000 mg. The average relative risk reductions for patients receiving PTAH or placebo in PALISADE were calculated and compared. Moreover, dose-specific analyses were conducted for patients who received PTAH based on different HTD values at trial exit. With consideration for sufficient sample size, the corresponding MEDs estimated at 600 mg and 1000 mg were reported in the analysis.

All the statistical analyses were performed using RStudio (v.1.1.453). As this was a post hoc analysis of previously published data, no institutional board review was required. This article

is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. The phase 3 trial PALISADE received IRB approval, was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments, and consent to participate was obtained from all participants.

RESULTS

Peanut Protein Exposure Distribution

The baseline data from all patients aged 4–17 years in PALISADE ($n = 496$) were used to estimate the daily peanut protein exposure distribution reflecting the exposure patterns for patients who practiced avoidance before the trial. The estimated probability density function assuming a maximum intake of 1500 mg peanut protein is shown in Fig. 1. For the Weibull, log-normal, and log-logistic distributions, patients would ingest less than 0.01 mg of peanut protein for 99.43%, 99.30%, and 99.02% of the time, respectively. The chance of being exposed to higher amounts was low: 0.01–1 mg (0.45%, 0.58%, and 0.86% for the Weibull, log-normal, log-logistic distributions, respectively), 1–10 mg (0.07%, 0.08%, and 0.08%), and 10 mg and above (0.04%, 0.04%, and 0.04%). The distributions of the MEDs estimated during the DBPCFC at screening (baseline) and trial exit are displayed in Figure S1a and S1b, respectively.

Risk Reduction

Only patients who completed the DBPCFC at trial exit and had HTD measured were included in the relative risk reduction analysis (PTAH: $n = 296$; placebo: $n = 116$) (Table 1). At baseline, the estimated annual risk of SAR was similar between the two treatment groups, ranging from 9.25 to 9.98% based on different

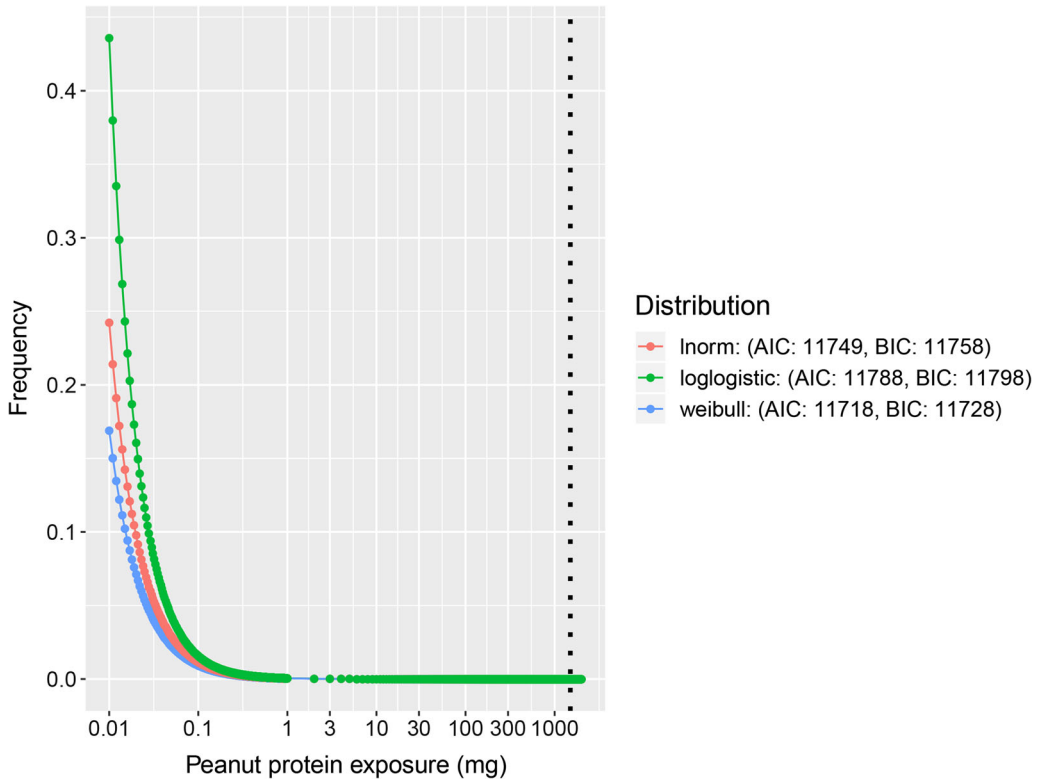

Fig. 1 Estimated probability density function of daily peanut protein exposure with a maximum intake of 1500 mg; *AIC* Akaike information criterion, *BIC* Bayesian information criterion, *lnorm* log-normal

Table 1 Estimated systemic allergic reaction risk reduction for patients receiving PTAH or placebo with a maximum intake of 1500 mg of peanut protein

Parametric function	PTAH ($n = 296$)			Placebo ($n = 116$)			PTAH–placebo
	Mean annual risk at baseline (%)	Mean annual risk at trial exit (%)	Mean relative risk reduction (%)	Mean annual risk at baseline (%)	Mean annual risk at trial exit (%)	Mean relative risk reduction (%)	Mean relative risk reduction (%)
Weibull	9.98	0.38	94.93	9.67	7.16	6.37	88.56
Log-normal	9.79	0.38	94.85	9.49	6.98	5.91	88.94
Log-logistic	9.54	0.37	94.74	9.25	6.75	5.42	89.32

PTAH peanut allergen powder-dnfp

parametric distributions for peanut protein exposure. At trial exit, there was a substantial difference between the mean annual risk for patients receiving PTAH (0.37–0.38%) versus placebo (6.75–7.16%). The absolute risk reductions (relative risk reduction) from baseline to trial exit among patients receiving PTAH were 9.60% (94.93%), 9.41% (94.85%), and 9.17% (94.74%) for Weibull, log-normal, and log-logistic distributions, respectively; for placebo, the values were 2.51% (6.37%,), 2.51% (5.91%), and 2.50% (5.42%), respectively. In order to prevent one SAR per year, 15–16 patients with peanut allergy would need to be treated with PTAH annually based on different parametric distributions for peanut protein exposure.

In the dose-specific analyses for PTAH-treated patients by HTD values at trial exit, the magnitude of relative risk reduction increased as HTD increased (Table 2). Based on the Weibull distribution, the average relative risk reductions were 88.57% and 97.16% when patients had HTD at 300 mg (estimated MED of 600 mg) and 600/1000 mg (estimated MED of 1000 mg), respectively. The results were consistent across the three parametric distributions.

When the maximum peanut protein exposure was assumed to be 2000 mg, the results of the exposure patterns and relative risk reductions were consistent with the primary analysis. The details are provided in Fig. S2 and Tables S1 and S2.

DISCUSSION

To the best of our knowledge, this is the first study to use clinical trial data to evaluate the risk reduction of SAR associated with accidental exposure for a pediatric population after 1 year of oral immunotherapy treatment for peanut allergy. Moreover, this is also the first study to

Table 2 Estimated systemic allergic reaction risk reduction for PTAH by estimated MED at trial exit with maximum intake at 1500 mg of peanut protein[a]

HTD at exit (mg)	Estimated MED at exit (mg)[b]	*n*	Mean relative risk reduction		
			Weibull (%)	Log-normal (%)	Log-logistic (%)
300	600	35	88.57	88.37	88.11
600	1000	63	97.16	97.08	96.99
1000	1000	187			

HTD highest tolerated dose, *MED* minimal eliciting dose, *NA* not applicable, *PTAH* peanut allergen powder-dnfp

[a] Included patients had any MED at baseline

[b] For patients whose HTD was 1000 mg, MED was not available and was conservatively assumed to be 1000 mg

evaluate the risk beyond unintended allergen residue from packaged food. As non-packaged food is not required to be labeled for the presence of allergens, accidental exposure by this route may be more likely than by packaged food in the real world [15]. The present estimate of peanut protein exposure considers both packaged and unpackaged food and better reflects real-world exposure routes. Using PALISADE clinical trial data, patients were estimated to ingest nearly zero peanut protein during their daily life (< 1% daily chance of ingesting more than 0.01 mg), which is logically consistent with how food-allergic patients would practice avoidance to prevent reactions [29]. Based on the estimated peanut protein exposure, the mean annual risk of SAR at the PALISADE trial entry was similar between the PTAH and placebo groups, ranging from 9.25 to 9.98%. This baseline annual risk, estimated based on the exposure distribution, was validated against prior studies and fell within their reported ranges [30–32]. In the PALISADE trial, accidental peanut protein exposure events occurred among 8.9% of patients in the active arm and 12.1% of patients in the placebo arm [19, 33]; thus the currently estimated annual risk is consistent with this range. The exposure events in the trial may also be somewhat overestimated compared to the real world, as patients were very closely monitored in the trial. Therefore, we believe that the peanut protein exposure distribution estimated in this study reflects a reasonable prediction of the real-world dietary experience of patients practicing peanut avoidance.

At trial exit, 1-year treatment with PTAH was associated with a substantial relative risk reduction of SAR of approximately 95%, underscoring its clinical benefits. For patients receiving placebo, the improvement was minimal, with an estimated relative risk reduction of 6%, which could be attributed to the placebo effect or reflect the small subset of peanut-allergic patients whose peanut tolerance threshold improves as they outgrow the disease. In addition, for PTAH-treated patients, the magnitude of the risk reduction increased from 88 to 97% as the estimated MED increased from 600 to 1000 mg. The results were robust to changes in various assumptions regarding the peanut protein exposure distribution and were consistent across the three parametric distributions examined.

The results of this study have several important implications. First, while the DBPCFC is recommended for measuring the efficacy of a food allergy treatment, it cannot provide direct inference on clinically meaningful outcomes. Based on well-established statistical methods, our study translates the DBPCFC results (i.e., increased tolerability of peanut protein) into a clinically relevant measurement (i.e., risk reduction of SAR) that is easily understood by physicians, patients, and caregivers. Our approach also presents an additional method to evaluate the impact of potential immunotherapies for food allergy based upon the risk of SAR, which is an important perspective for all stakeholders when considering a treatment's benefits. Second, this study enables direct estimations of accidental peanut protein exposure by using clinical trial data to consistently evaluate both exposure patterns and risk prediction, instead of relying on external data sources. More importantly, the estimations are not limited to a particular type of peanut protein food source, but are inclusive of both packaged and unpackaged foods. Third, the use of different parametric distributions and scenarios of maximum intake values in this study provides a plausible range of the risk estimates. The results are largely insensitive to the choice of parametric functions or maximum intake assumptions, indicating that the analyses are robust. Lastly, the analytical framework used in the current study can be easily extended to other types of food allergies for the purpose of risk quantification.

The current study used a conservative imputation approach for patients who did not experience dose-limiting symptoms at 1000 mg, which would underestimate the risk reduction especially for PTAH-treated patients, as more than half of the PTAH-treated patients fell into this category. When assuming a post-desensitization MED of > 1500 mg for these patients, the relative risk reduction associated with PTAH increased to 97%. In addition, this study focused on patients who completed the exit

DBPCFC in PALISADE. For patients who dropped out during the study, the unique food challenge study design and different dropout reasons that were not necessarily outcome-driven (e.g., 50% of withdrawals were due to concerns from a parent/guardian or other reasons) made MED imputation impossible. However, as dropout patients were similar to the completers in terms of demographics and prior allergy history, the study results are not expected to substantially differ between the completers and dropout patients, if they had completed 1 year of treatment. The adverse events (AEs) noted in the trial have been previously observed during oral immunotherapy use [34, 35]. Although an analysis of the intent-to-treat (ITT) population is of interest for most trial-based studies, the purpose of the current study was to understand what the risk–benefit is for those who completed active treatment in PALISADE. This is a meaningful insight for doctors, patients, and payers when considering the benefit of PTAH for peanut allergy. While a treatment's safety is also an important factor to consider, the present analysis focused solely on efficacy. However, in PALISADE, ~ 96% of all treatment-emergent AEs were mild to moderate among PTAH-treated patients. Additionally, just 14% of treatment-emergent AEs were systemic allergic reactions, and nearly all these were also mild or moderate (see Supplementary Table S3 in the trial publication [19]). Future studies using a novel approach that combines the two facets of treatment (both safety and efficacy) is warranted.

Several prior studies have quantified the risk reduction associated with immunotherapy for peanut-allergic patients. Baumert et al. (2018) and Remington et al. (2018) evaluated the risks and benefits associated with a general immunotherapy for hypothetical peanut-allergic individuals based on hypothetical MEDs among the US and European populations using a Monte-Carlo simulation method [22, 23]. Another study by Remington et al. (2019) evaluated the risk reduction associated with epicutaneous immunotherapy (EPIT) for pediatric patients with peanut allergy [28]. All three studies selected a few packaged foods and used national survey data to inform patients' peanut protein exposure. Recently, two studies by Remington et al. (2020) used unpackaged food of restaurant meals for risk quantification via peanut residues on the shared kitchen equipment from Asian food [36, 37]. In contrast, the present analysis is based on patients' baseline characteristics, which reflect their real-life exposure. Thus, the estimated peanut protein exposure in our study would not be limited to certain food sources. Another strength is the consistent use of clinical trial data to avoid potential bias from the heterogeneity of different data sources. As reported by Remington et al. (2019), the risks varied across different food categories [28]. In that study, the baseline annual risk was 3.8% when peanut protein came from salty snacks but was much higher (i.e., 11.3%) for ice cream.

While Baumert et al. (2018) and Remington et al. (2018, 2020) used a Monte Carlo simulation method for risk assessment, our study employed an interval-censored survival analysis with the maximum likelihood estimation approach. This method is considered the most appropriate statistical approach in allergy studies, and has been applied in prior studies such as Taylor et al. (2009) and Remington et al. (2019) [26, 28]. Remington et al. (2019, 2020) used phase 3 trial data, where 35.3% were responders after 12 months of EPIT with MED at 300/1000 mg (HTD of 100/300 mg), and reported risk reductions of 71–86%, respectively. The results varied by the choice of peanut protein food sources, and the uncertainty could increase when different food was considered. On the other hand, the current study used data from PALISADE, where 67.2% of participants were responders after 12 months of PTAH, with HTD $\geq$ 600 mg, and an estimated 93–95% reduction in SAR due to accidental exposure to various types of food sources from patients' daily diet.

Limitations

This study is subject to several limitations. First, the study estimated the accidental peanut protein exposure based on PALISADE data. The trial only recruited participants with dose-limiting

symptoms at a dose of ≤ 100 mg during the screening DBPCFC, while approximately 50% of the general peanut-allergic population would have a reaction at doses > 100 mg [38]. Thus, the results were estimated from a population that was relatively more sensitive to peanut protein, and might not be representative of the real-world peanut protein intake for the overall pediatric population with peanut allergy. Second, we assumed a parametric distribution for peanut protein exposure, which may not reflect the true exposure patterns. However, the resultant baseline absolute risk estimates (i.e., 9–10%) are close to values reported in the literature [30–32], lending credibility that the present parametric assumption may be valid and can represent real-world accidental exposure to some extent. Third, this study extrapolated the risk reduction among patients who completed the exit food challenge instead of the ITT population, and thus did not include those who dropped out during the study, which may lead to some estimation bias. However, the nature of the two-stage analysis and similar patient characteristics between completers and dropout patients made the results generally robust. Studies examining the risk reduction among the ITT population of PALISADE may be warranted in the future. Fourthly, the results were based on PTAH use over 12 months, when about half of the patients did not experience dose-limiting symptoms at 1000 mg and their MED was conservatively assumed to be 1000 mg. This assumption would have resulted in an underestimation of the risk reduction, as patients may increase their peanut protein threshold even further with continued treatment and thus experience a greater risk reduction. Fifth, this study estimated SAR caused by accidental exposure to peanut protein and did not examine iatrogenic reactions that are expected in a minority of patients related to the PTAH treatment itself. This could lead to overestimation of the overall risk reduction benefit associated with PTAH. However, due to the difference in the nature of iatrogenic reactions versus accidental SAR, iatrogenic reactions triggered by the oral immunotherapy are expected to some extent. These reactions are anticipated to happen shortly after treatment and are manageable in a controlled environment (e.g., at home) under the supervision of patients' caregivers. Together with accidental SAR, understanding iatrogenic reactions is critical for the shared decision-making process and in assessing the benefits of different treatment options. Thus, future real-world observational research with long-term follow-up data, taking iatrogenic reactions into consideration, as well as real-world studies of pediatric patients with peanut allergy, are important to refine the risk reduction associated with PTAH.

CONCLUSIONS

This is the first study to use clinical trial data to evaluate the risk reduction associated with accidental peanut protein exposure after 1 year of treatment with PTAH oral immunotherapy among children with peanut allergy and considering all routes of potential allergen exposure. The results indicate that PTAH use is expected to be associated with a substantial reduction in the risk of SAR (by at least 95%) and that the magnitude of risk reduction increased with patients' ability to tolerate higher challenge doses at the exit DBPCFC. The results were robust to changes in various assumptions regarding the peanut protein exposure distribution, and were consistent across the three parametric distributions. Finally, the analytical framework used in the current study could be easily extended to other food allergy therapies to quantify their risk reduction benefits.

ACKNOWLEDGEMENTS

Funding. Sponsorship for this study, the journal's Rapid Service Fee and Open Access Fee were funded by Aimmune Therapeutics.

Medical Writing, Editorial, and Other Assistance. Medical writing assistance was provided by Shelley Batts, PhD, an employee of Analysis Group, Inc. Funding for this assistance was provided by the sponsor. The authors

would also like to acknowledge Nadine Zawadzki of the University of Southern California for assisting in the literature review and scope of the study.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authors' Contributions. All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Xinglei Chai, Jenny Zhou, Rajeev Ayyagari, and Eric Wu. The first draft of the manuscript was written by Shengsheng Yu, Xinglei Chai, and Jenny Zhou, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Prior Presentation. Portions of this research were presented at the 2020 ISPOR conference held virtually during May 18–20, 2020.

Disclosures. Stephen Tilles, Shengsheng Yu, Alex Smith, Dan Robison, and Sarah M. Donelson are employees of Aimmune Therapeutics and hold stock/options. Steve Hass is an employee of H.E. Outcomes, LLC and is a consultant to Aimmune Therapeutics. Eric Wu, Xinglei Chai, Jenny Zhou, and Rajeev Ayyagari are employees of Analysis Group, Inc., which has received consulting fees from Aimmune Therapeutics. Jun S. Liu received research funding from Aimmune Therapeutics for this study.

Compliance with Ethics Guidelines. As this was a post-hoc analysis of previously published data, no institutional board review was required. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. The phase 3 trial PALISADE received IRB approval, was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments, and consent to participate was obtained from all participants.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available as they will be disclosed in future publications.

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