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Sustained Unresponsiveness to Peanut After Long-Term Peanut Epicutaneous Immunotherapy

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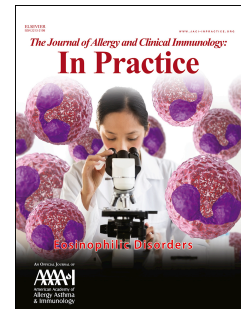
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Title:

Sustained Unresponsiveness to Peanut After Long-Term Peanut Epicutaneous Immunotherapy

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Declaration of Funding and Conflict of Interest Statement:

Dianne E. Campbell, Todd D. Green, Aurélie Peillon, and Hugh A. Sampson are employees of DBV Technologies. Terri Brown-Whitehorn is a DBV Technologies grant recipient, clinical advisory board member, and consultant. Frédéric de Blay reported receiving grants and/or personal fees from Stallergenes Greer, Chiesi, ALK, Mundipharma, and Novartis, as well as serving as a board member for Stallergenes Greer, Novartis, ALK, Mundipharma, Meda Pharma, Boehringer Ingelheim, and AstraZeneca. Jonathan M. Spergel reports board membership from the American Partnership for Eosinophilic Disorders (APFED) and the International Food Protein-Induced Enterocolitis Syndrome (FPIES) Association; consultancy fees from DBV Technologies, Sanofi/Regeneron, and Medscape; speaker fees from Abbott; and grants to his institution from the National Institutes of Health and End Allergies Together and Aimmune.

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Clinical Implications:

Sustained unresponsiveness to peanut, at a level that may protect from many clinical allergic reactions related to accidental exposure, has been observed in a subset of participants following 2 to 3 years of successful epicutaneous immunotherapy.

Peanut allergy is a common and largely persistent food allergy with no known cure. Globally, widespread clinical trials are in progress that seek to improve the lives of children and adults with peanut allergy using desensitization to peanut via a variety of routes, including oral, sublingual, subcutaneous, intranodal, and epicutaneous.¹ Additionally, the US Food and Drug Administration recently granted approval of a form of peanut oral immunotherapy (OIT).

Most immunotherapy trials to date have focused on efficacy during or immediately at the completion of therapy. However, the question of whether treatment effect persists once the therapy has been completed and discontinued (and while peanut avoidance otherwise continues) remains largely unclear.

We sought to examine whether there was evidence of a longer-lasting effect of therapy, often described as sustained unresponsiveness (SU), and more recently as remission,² following 2 or more years of epicutaneous peanut immunotherapy (EPIT) from a subset of participants from the OLFUS-VIPES phase 2b study.³ In the VIPES randomized controlled trial, the optimal dose, safety, and efficacy of 12 months of daily peanut EPIT (DBV712) in peanut-allergic subjects aged 6-55 years who had a baseline eliciting dose (ED) of ≤ 300 mg of peanut protein was assessed, followed by an open-label extension of up to 24 months on EPIT (OLFUS-VIPES).³ At the end of the open-label study, subjects who showed no objective symptoms (meeting stopping criteria) during a double-blind placebo-controlled food challenge (DBPCFC) at equal to or greater than a cumulative peanut dose of 1440 mg were eligible to enroll in an SU assessment. For those subjects, a further DBPCFC was conducted 2 months after cessation of peanut EPIT with continued strict peanut avoidance.

As previously reported, 221 subjects enrolled in the VIPES study (of which 56 received DBV712 250 µg from randomization) and 171 enrolled in the OLFUS-VIPES extension study; within 6 months of starting the open-label extension study, all subjects were transitioned to DBV712 250 µg for the remainder of their participation.³ One hundred twenty-four subjects underwent a DBPCFC following a total of 36 months study duration, of which 29 (23%) had no objective symptoms to a cumulative dose of 1440 mg. This included 21 children aged 6-11 years and 8 adolescents/adults aged 12-55 years at VIPES study entry (**Table 1**).

Of these 29 subjects, 25 elected to undergo the pre-specified SU assessment according to the study protocol and 20 (80%) maintained desensitization to at least 1440 mg of peanut at 2 months follow-up DBPCFC (ie, had no objective symptoms to a cumulative dose of 1440 mg) (**Table 1, Figure 1**). All 25 subjects who underwent SU assessment reached a cumulative reactive dose (CRD) of ≥1440 mg at the Month 2 SU DBPCFC, reflecting a substantial sustained improvement from baseline CRD (median 144 mg). There was no significant change in peanut-IgE (median 8.06; 7.72 kU_A/L) or peanut IgG4 (median 2.03; 1.88 mg/L) over the 2 months off therapy at Month 36 and 38, respectively, in those 25 subjects.

Overall, subjects who successfully achieved SU were predominantly male and had a lower baseline median peanut-IgE compared with the whole VIPES and OLFUS cohorts (**Table 1**). SU was achieved across both age groups, and although there was a greater proportion of children who met criteria for SU assessment, of those eligible, 14/19 (73.7%) children aged 6-11 years and 6/6 (100%) adolescents/adults attained SU. It is difficult to determine whether there were any characteristics that discriminated between those 5 subjects who, having met the SU assessment criteria, were not able to sustain their tolerance above 1440 mg (over the 2-month cessation of therapy while avoiding peanut) compared to the 20 who achieved SU, as the numbers in each group were too small; however, it is worth noting that these subjects still reached an ED of 1000 mg (CRD of 1440 mg) at the 38-month SU DBPCFC. In addition, there were 6 subjects whose CRD decreased from Month 36 to Month 38, but remained greater than 1440 mg (range 5040-6040 mg at Month 36 to 2440-5040 mg at Month 38), and 3 subjects whose CRD increased from Month 36 to Month 38 (range 3040-3840 mg at Month 36 to 4040-5040 mg at Month 38) (**Figure 1**).

Emerging murine data suggest that response to EPIT is driven primarily by T regulatory cells (Tregs) with no allergen-driven effector cell desensitization, suggesting both a different mechanism of action of EPIT compared with immunotherapy delivered by alternative routes, and a mechanism by which SU following cessation of immunotherapy might occur.⁴ This is supported by hypermethylation of the Gata3 promoter and hypomethylation of the Foxp3 promoter on Tregs in murine EPIT models.⁵ It is therefore plausible that the duration of therapeutic effect with EPIT, as suggested by animal models, may lead to a slower achievement of maximal response, but more sustained duration of desensitization, with effects continuing after therapy has ceased.⁴

There are several limitations to the data. Firstly, SU was only assessed in subjects who attained desensitization following at least 24 months of therapy with EPIT to a cumulative dose of 1440 mg of peanut (approximately 5-6 peanut kernels). In addition, SU was defined in the protocol specifically as described above, as unresponsiveness to 1440 mg of peanut protein or greater and did not require completion of the entire DBPCFC. In contrast to SU or remission definitions used more recently, this allowed for subjects to experience CRD decreases and still meet the protocol definition of SU with a threshold of 1440 mg or higher. Tolerance to the highest DBPCFC dose was not required to achieve SU. In addition, whether subjects who attained less marked improvements in their peanut ED would have also continued to be desensitized over a similar time period off therapy, at a lower ED level, is uncertain. The baseline characteristics of subjects who were eligible for SU assessment were

generally similar to the overall cohort, including the amount of peanut that initially triggered the allergic reaction at DBPCFC and the severity of the reaction (as measured by epinephrine usage). They differed in having a higher proportion of males and lower baseline peanut-IgE. Peanut-IgG4 at any time point did not distinguish between those who met eligibility criteria for the SU assessment, nor those who achieved SU (**Table 1**). However, OLFUS-VIPES was not primarily designed to assess SU, thus the sample size is too small to detect differences between those 20 subjects who achieved SU compared to the 5 who did not, and comparisons should be interpreted with some caution.

Finally, the concept of SU itself is under some scrutiny.² Exactly what allergic reactivity, as assessed by food challenge after a relatively short period (2 months) off therapy, means for longer-term tolerance is unclear. Anecdotal follow-up reports of EPIT (where 12 of 15 patients at Children's Hospital of Philadelphia introduced peanut-containing foods on a daily basis at amounts recommended based on their final DBPCFC following OLFUS-VIPES completion),⁶ and other forms of peanut immunotherapy such as OIT and OIT with adjuvant therapy, suggest that some SU possibly translates into longer-term desensitization, and in some cases ad lib peanut consumption.^{7,8} These reports should be viewed with cautious optimism, given the likely skewed subset of the total study populations these reports represent; indeed, it is important to recognize that SU may wane with increasing time of avoidance/off therapy, as has been demonstrated in studies of peanut OIT.⁹

Overall, our findings support the notion that SU to peanut protein following long-term therapy with EPIT is achievable for a subset of peanut-allergic patients. Whether these effects last longer than 2 months, and whether they can be extrapolated to the wider study population, remains to be determined. Furthermore, in future studies of EPIT it will be important to robustly identify any baseline or on-therapy characteristics that may be associated with a higher propensity to short-term and longer-term SU.

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Figure Legend**Figure 1. Cumulative Reactive Dose (CRD) Over Time in Subjects Opting-In to Sustained Unresponsiveness Assessment (N=25).**

Cumulative reactive dose is shown at Month 0 (VIPES baseline), Month 12 (OLFUS-VIPES baseline), Month 24, Month 36, and Month 38 for the 25 subjects opting-in to the sustained unresponsiveness assessment. Dotted lines represent subjects aged ≥ 12 years. Lines with markers represent the 5 subjects who did not achieve sustained unresponsiveness (ie, did not maintain desensitization to a cumulative reactive dose of ≥ 1440 mg following 2 months off treatment). S=subject.

Table 1: Characteristics of Participants at Study Entry, Month 36 and 38 Assessments

	VIPES (n=221)	SU Eligible (n=29)	SU Assessment (n=25)	Achieved SU (n=20)
Age, years* (median, IQR)	11.0 (8.0, 16.0)	10.0 (7.0, 12.0)	10.0 (7.0, 11.0)	10.0 (8.0, 13.0)
6-11 years (n, %)	113 (51.1%)	21 (72.4%)	19 (76.0%)	14 (70.0%)
12-55 years (n, %)	108 (48.9%)	8 (27.6%)	6 (24.0%)	6 (30.0%)
Male (n, %)	138 (62.4%)	22 (75.9%)	19 (76.0%)	17 (85.0%)
Initial allocation in VIPES (n)				
Placebo	48	3	3	3
50 µg	44	6	5	5
100 µg	41	11	10	7
250 µg	38	9	7	5
Peanut IgE, kU _A /L (median, IQR)				
Baseline*	78.90 (17.8, 217.25)	19.80 (5.78, 70.80)	13.90 (5.09, 63.80)	8.09 (3.37, 56.45)
Month 36 [†]	NA	9.16 (3.83, 44.80)	8.06 (2.77, 36.10)	6.46 (1.45, 42.40)
Month 38 (SU assessment) [†]	NA	NA	7.72 (2.61, 33.30)	6.14 (1.94, 34.95)
Peanut IgG4, mg/L (median, IQR)				
Baseline*	0.59 (0.29, 1.48)	0.60 (0.23, 1.05)	0.60 (0.23, 1.27)	0.53 (0.14, 1.16)
Month 36 [†]	NA	2.03 (0.90, 9.24)	2.03 (0.85, 9.24)	1.62 (0.49, 4.08)
Month 38 (SU assessment) [†]	NA	NA	1.88 (0.78, 7.27)	1.26 (0.56, 4.35)
SPT mean wheal size, mm (median, IQR)*	11.5 (9.5, 14.0)	11.0 (10.0, 14.5)	11.0 (9.5, 15.0)	10.3 (9.0, 14.5)
Baseline CRD, mg (median, IQR)*	144 (44, 444)	144 (144, 444)	144 (144, 444)	194 (144, 444)
History of asthma (%)*	58.8%	55.2%	60.0%	55.0%
Use of epinephrine at initial DBPCFC (n, %) [‡]	93 (42.1%)	11 (37.9%)	10 (40.0%)	8 (40.0%)

DBPCFC=double-blind placebo-controlled food challenge; IQR=interquartile range; SU =sustained unresponsiveness (defined as showing no objective symptoms meeting stopping criteria to a cumulative dose of 1440 mg after 2 months).

*At VIPES entry.

[†]Prior to DBPCFC.

[‡]At least one dose of epinephrine at initial VIPES DBPCFC.

Figure 1. Cumulative Reactive Dose (CRD) Over Time in Subjects Opting-In to Sustained Unresponsiveness Assessment (N=25)