Original Article

Peanut-Specific IgG4 and IgA in Saliva Are Modulated by Peanut Oral Immunotherapy

Johanna M. Smeekens, PhD[a,b], Carolyn Baloh, MD[c], Noha Lim, PhD[c], David Larson, PhD[c], Tielin Qin, PhD[c], Lisa Wheatley, MD, MPH[d], Edwin H. Kim, MD, MS[a,b], Stacie M. Jones, MD[e], A. Wesley Burks, MD[a,b], and Michael D. Kulis, PhD[a,b] *Chapel Hill, NC; Bethesda, Md; and Little Rock, Ark*

What is already known about this topic? Serum peanut-specific immunoglobulin G4 (IgG4) and IgA are significantly increased after peanut oral immunotherapy, but do not correlate to an individual's likelihood of success on therapy. Immunoglobulin responses have yet to be studied at the oral mucosal surface.

What does this article add to our knowledge? Peanut oral immunotherapy induces substantial increases in allergen-specific IgG4 and IgA in saliva. Salivary peanut IgA is higher at baseline in subjects that do not achieve desensitization, suggesting the increase during oral immunotherapy is beneficial for desensitization.

How does this study impact current management guidelines? These data provide insight into oral immunotherapy–induced mucosal responses and suggest utility of these easily obtained samples for biomarker development.

BACKGROUND: Antigen-specific immunoglobulin responses have yet to be studied at the oral mucosal surface during peanut oral immunotherapy (PnOIT).

OBJECTIVE: We aimed to quantify salivary peanut-specific IgG4 (PNsIgG4) and IgA (PNsIgA) and total IgG4 and IgA in participants from the Immune Tolerance Network's IMPACT study, a phase 2 PnOIT trial.

METHODS: Peanut-allergic children, aged 12 months to younger than 48 months at screening, were enrolled and randomized to PnOIT or placebo oral immunotherapy (OIT) for 134 weeks. Per-protocol analysis included 69 PnOIT and 23 placebo participants. Double-blind, placebo-controlled food challenges were conducted at weeks 134 and 160 to assess desensitization and remission, respectively. Saliva samples were collected at baseline and 30, 82, 134, and 160 weeks to quantify PNsIgG4, PNsIgA, and total IgG4 and IgA.

RESULTS: Participants who received PnOIT experienced significant increases in PNsIgG4 in saliva, whereas participants on placebo did not ($P < .01$ at all time points). The PNsIgA/total IgA ratio was also significantly increased in participants treated with PnOIT when compared with those receiving placebo at 30 and 82 weeks ($P < .05$). During PnOIT, desensitized participants had increased PNsIgA that plateaued, whereas the not desensitized/no remission group did not change over time. Interestingly, when the PnOIT group was evaluated by clinical outcome, PNsIgA was higher at baseline in the not desensitized/no remission group than in the desensitized/remission group ($P < .05$).

CONCLUSIONS: PnOIT induces substantial increases in allergen-specific IgG4 and IgA in saliva. These data provide insight into OIT-induced mucosal responses and suggest the utility of these easily obtained samples for biomarker development. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;■:■-■)

Key words: *Peanut allergy; Oral immunotherapy; IgA; IgG4; Saliva*

INTRODUCTION

Peanut allergy is a growing public health concern affecting 2% of the U.S. population.[1] The current standard of care is

[a]Department of Pediatrics, Division of Allergy and Immunology, UNC School of Medicine, Chapel Hill, NC
[b]UNC Food Allergy Initiative, Department of Pediatrics, UNC School of Medicine, Chapel Hill, NC
[c]Immune Tolerance Network, Bethesda, Md
[d]National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health, Bethesda, Md
[e]Department of Pediatrics, University of Arkansas for Medical Sciences and Arkansas Children's Hospital, Little Rock, Ark

This research was performed as a project of the Immune Tolerance Network, an international clinical research consortium headquartered at the Benaroya Research Institute and supported by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) under Award Number UM1AI109565. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. J. M. Smeekens is funded by a T32 Allergy/Immunology Training Grant (AI007062) through Duke University and University of North Carolina at Chapel Hill.

Conflicts of interest: J. M. Smeekens has received funding from an NIH T32 training grant. S. M. Jones reports grants from NIH-NIAID, Food Allergy Research & Education (FARE), Aimmune Therapeutic, DBV Technologies, Astellas, Inc., Sanofi, Inc., Regeneron, Inc., and Genentech, Inc.; and personal fees from Food Allergy Research and Education, EMMES Corporation, and Aimmune Therapeutics. M. D. Kulis has received research support from NIH and the Department of Defense (DoD), and consulting fees from Ukko. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication June 7, 2022; revised July 7, 2022; accepted for publication July 27, 2022.

Available online ■■

Corresponding author: Michael D. Kulis, PhD, 116 Manning Dr., Mary Ellen Jones, Room 3304D, Chapel Hill, NC 27599. E-mail: Mike.kulis@unc.edu.

2213-2198

https://doi.org/10.1016/j.jaip.2022.07.030

Abbreviations used
DBPCFC- Double-blind placebo-controlled food challenge
IgA- IgE
IgG4- Immunoglobulin A
E- G4
ITN- Immune Tolerance Network
OIT- Oral immunotherapy
PnOIT- Peanut oral immunotherapy
PNsIgA- Peanut-specific IgA
PNsIgE- Peanut-specific IgE
PNsIgG4- Peanut-specific IgG4

avoidance and ready access to epinephrine, although food- specific immunotherapies are actively being investigated. Oral immunotherapy (OIT) has been studied for the last 15 years,[2,3] and is an effective treatment option for peanut allergy. Indeed, 1 peanut oral immunotherapy (PnOIT) product, Palforzia, recently gained U.S. Food and Drug Administration (FDA) approval after a successful phase 3 study.[4] The biological mechanisms of PnOIT remain unclear, but consistent changes in systemic immunoglobulin levels have been observed.[5] Notably, peanut-specific immunoglobulin G4 (PNsIgG4) in plasma increases sharply within the first few months with some studies also showing increases in peanut-specific IgA (PNsIgA) throughout therapy.[6,7] Peanut-specific IgE (PNsIgE) increases for the first 6 months on OIT, and then decreases below baseline levels after approximately 12 months.[8,9] Whereas these changes are consistently observed with treatment, they have had little success when used as biomarkers to predict OIT outcomes.[10] However, because OIT is administered at the oral and gastrointestinal mucosal surfaces, antigen-specific immunoglobulin responses at these sites may be more informative.

Oral tolerance is a naturally occurring process in nonallergic individuals that typically results in elevated levels of serum antigen-specific IgG4 and IgA.[11] For example, in the Learning Early About Peanut Allergy (LEAP) trial, early introduction of peanut in infants who were protected from peanut allergy resulted in substantial increases in PNsIgG4, not seen in the infants avoiding peanut.[12] In a separate study, serum antigen-specific IgA2 was shown to play a role in tolerance in subjects who outgrew their egg allergy.[13] Collectively, these studies suggest antigen-specific IgG4 and IgA may dampen IgE responses. Food allergen−specific immunotherapies are employed to induce increased production of antigen-specific IgG4 and IgA, which have been demonstrated to block effector cell degranulation.[7,14,15] Whereas these effects have been demonstrated with serum antigen-specific immunoglobulins, the effects at mucosal surfaces are not well-defined.

To evaluate local immune responses, we utilized samples from the Immune Tolerance Network's (ITN's) IMPACT study, a phase 2 randomized, placebo-controlled trial of PnOIT.[16] Briefly, the IMPACT trial was designed to study desensitization and remission after PnOIT. Specifically, children aged 12 months to younger than 48 months with double-blind, placebo-controlled food challenge (DBPCFC)−confirmed peanut allergy were assigned to PnOIT (n = 96) or placebo OIT (n = 50) for 134 weeks. Participants were assessed for desensitization and remission by DBPCFCs at week 134 (end of treatment) and 160 (after 6 months of avoidance), respectively. The 69 participants who completed the protocol (ie, the per-protocol population) and passed the DBPCFC at weeks 134 and 160 were categorized as desensitized/remission (n = 19), participants that passed the DBPCFC at week 134 but failed at week 160 were categorized as desensitized/no remission (n = 40), and participants that did not pass the DBPCFC at week 134 were categorized as not desensitized/no remission (n = 10) (Table I). To assess the immunological response to PnOIT at the oral mucosal surface and its potential to predict treatment outcomes, we aimed to quantify salivary PNsIgG4 and PNsIgA and total IgG4 and IgA in the ITN IMPACT trial and compare these with their sera counterparts.

METHODS

Clinical trial description

The ITN IMPACT clinical trial (NCT01867671) information can be found elsewhere.[16]

Saliva samples

Saliva was collected either by suction with a syringe or by spitting directly into a cryovial after first rinsing the mouth with water or a damp washcloth. Saliva samples were then frozen and stored long term at −80°C until analysis. Samples were deidentified and researchers measured IgA and IgG4 while blinded.

IgG4 and IgA enzyme-linked immunosorbent assays

For PNsIgG4 and total IgG4 enzyme-linked immunosorbent assays (ELISAs), 96-well plates were coated with 2 μg/mL of antihuman IgG4 (clone G17-4, BD Biosciences, San Jose, CA) for standard curves or 20 μg/mL peanut protein (extracted as described previously[17]) for saliva samples. Wells were blocked with 2% bovine serum albumin in phosphate-buffered saline with 0.05% Tween 20. Saliva samples were diluted 1:10 for PNsIgG4 and 1:20 for total IgG4. Standard curves were generated with native human IgG4 protein (Abcam, Cambridge, MA) ranging from 0.24 to 250 ng/mL. Samples and standards were detected with a 1:1000 dilution of antihuman IgG4 Fc-HRP (clone HP6025; Southern Biotech, Birmingham, AL). Plates were developed using tetramethyl benzidine (TMB) (SeraCare, Milford, MA); the reaction was stopped by using 1% HCl (SeraCare), and the results were read at 450 nm by using a microplate spectrophotometer (BioTek, Winooski, VT).

For PNsIgA and total IgA ELISAs, 96-well plates were coated with 2 μg/mL of antihuman IgA1/IgA2 (clone G18-1; BD Biosciences, San Jose, CA) for standard curves or 20 μg/mL peanut protein for saliva samples. Wells were blocked with 2% bovine serum albumin in phosphate-buffered saline with 0.05% Tween 20. Saliva samples were diluted 1:50 for PNsIgA and 1:20,000 for total IgA. Standard curves were generated with purified human IgA (Bethyl Labs, Montgomery, TX) ranging from 0.6 to 60 ng/mL. Samples were detected with a 1:1000 dilution of antihuman IgA-HRP (Southern Biotech). Plates were developed using TMB (SeraCare, Milford, MA); the reaction was stopped by using 1% HCl (SeraCare), and the results were read at 450 nm by using a microplate spectrophotometer (BioTek, Winooski, VT).

Serum IgE, IgA, and IgG4 quantification

Serum immunoglobulins were quantified by the ImmunoCAP 1000 System (Phadia-ThermoFisher, Waltham, MA) as previously described.[16]

Statistics

Saliva and serum antibody data were analyzed for participants in the per-protocol population who were study-compliant through the

TABLE I. Demograpopt_Chics of subjects on PnOIT*

Demographic category	Desensitized/remission (n = 19)	Desensitized/no remission (n = 40)	Not desensitized/no remission (n = 10)
Age (mo)	30 (24–38.4)	39.6 (35.7–46.8)	40.8 (36.9–41.7)
Sex			
Female	7 (37%)	11 (28%)	3 (30%)
Male	12 (63%)	29 (72%)	7 (70%)
Race			
Asian	3 (16%)	6 (15%)	2 (20%)
Black	0 (0%)	1 (2%)	0 (0%)
Mixed	2 (11%)	9 (22%)	2 (20%)
White	14 (74%)	24 (60%)	6 (60%)
Other food allergy			
At screening	12 (63%)	21 (52%)	7 (70%)
At end of study	15 (79%)	25 (62%)	8 (80%)
PNsIgE (serum, kU/L)	16.5 (10.38-46.5)	69.5 (38–196.75)	135.4 (50.5–316.75)
Total IgE (serum, kU/L)	486 (192.5–703.75)	400.5 (192.5–617.75)	452 (247.25–772.5)

IQR, Interquartile range.
*Data are n (%) or median (IQR).

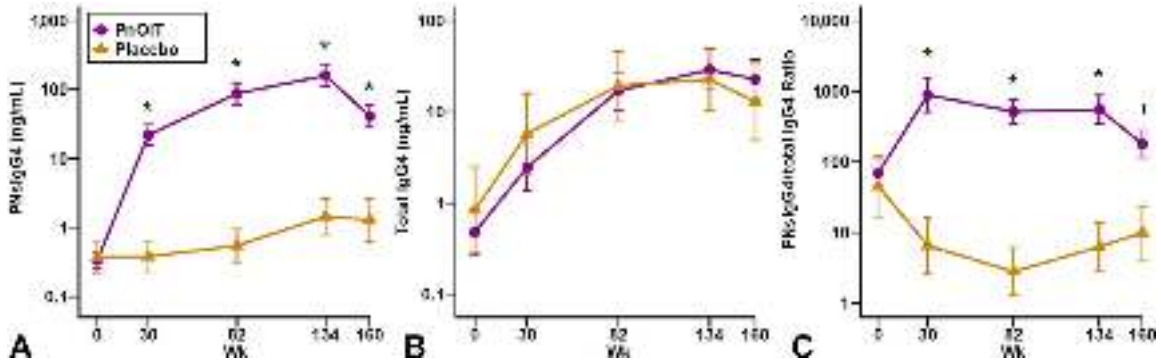

FIGURE 1. PNsIgG4 and total IgG4 in saliva. (**A**) PNsIgG4, (**B**) total IgG4, and (**C**) PNsIgG4/total IgG4 ratio throughout the course of peanut (purple) or placebo (gold) OIT. Data are shown as mean ± standard error of the mean. *$P < .01$; †$P < .05$.

avoidance phase and had an evaluable blinded DBPCFC at the end of the maintenance and avoidance phases (per-protocol population for the secondary end point). For comparisons between placebo and PnOIT groups, a linear mixed model was used with adjustment for baseline levels. For comparisons among PnOIT outcome groups, a linear mixed model was used without adjustment for baseline levels. The threshold for significance was P less than 0.05 (2-sided). All analyses were performed with SAS Version 9.4 (SAS Institute Inc., Cary, NC) and R version 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Salivary IgG4 during PnOIT treatment and avoidance

Saliva and serum samples were collected at baseline and at 30, 82, 134, and 160 weeks for quantification of salivary PNsIgG4 and total IgG4, and serum PNsIgG4. Participants receiving PnOIT demonstrated significant increases in PNsIgG4 in saliva, whereas participants receiving placebo did not (placebo vs PnOIT; $P < .01$ at all time points; Figure 1, *A*). After therapy was discontinued at week 134, PNsIgG4 sharply decreased in the PnOIT group. Total IgG4 was similar between placebo and PnOIT groups at baseline and increased in both treatment groups over time (Figure 1, *B*). When looking at the ratio of PNsIgG4 to total IgG4 in the PnOIT group, there was a sharp increase at week 30, which plateaued through the remaining maintenance period and decreased during avoidance (weeks 134–160) (Figure 1, *C*). The PNsIgG4 to total IgG4 ratio did not increase in the placebo group during the trial.

For the 69 participants who completed the protocol, when stratified by clinical outcome, a significant difference was noted in PNsIgG4 between the desensitized/remission and the desensitized/no remission groups at week 82 (Figure 2, *A*). For total IgG4, the not desensitized/no remission group trended toward lower levels throughout the course of treatment, and when therapy was stopped, there were statistically lower levels of total IgG4 between the not desensitized/no remission and the desensitized/no remission groups at week 160 (Figure 2, *B*). Taking into account the ratio of PNsIgG4 to total IgG4, the desensitized/remission group increased from baseline, and remained constant throughout the course of therapy, in comparison with the other groups in which, on average, there was an increase at week 30 and it remained elevated throughout treatment at week 134 (Figure 2, *C*). Interestingly, the desensitized/

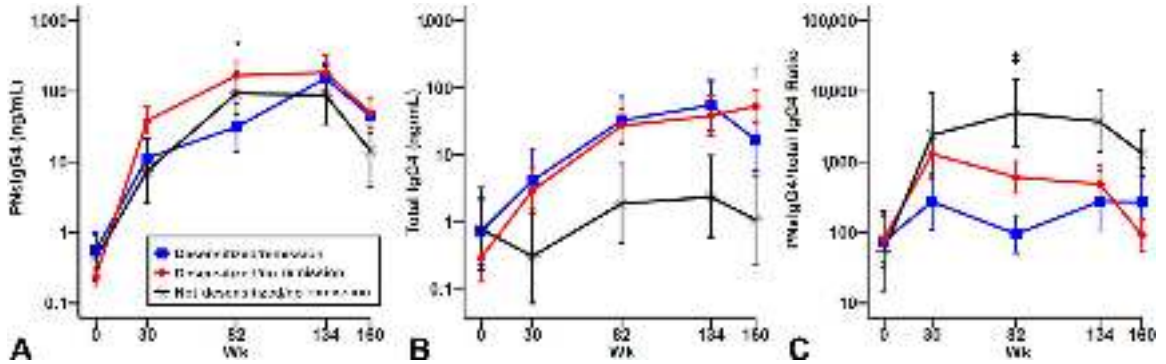

FIGURE 2. PNsIgG4 and total IgG4 in saliva by clinical outcome. (**A**) PNsIgG4, (**B**) total IgG4, and (**C**) PNsIgG4/total IgG4 ratio in desensitized/remission (blue), desensitized/no remission (red), and not desensitized/no remission (black) OIT participants. Data are shown as mean ± standard error of the mean. *$P < .05$ for desensitized/remission versus desensitized/no remission; †$P < .05$ for desensitized/no remission versus not desensitized/no remission; ‡$P < .05$ for desensitized/remission versus not desensitized/no remission.

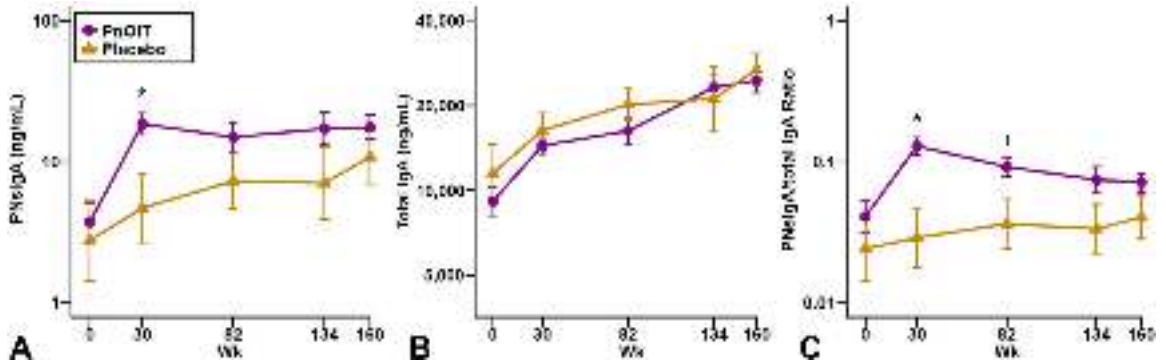

FIGURE 3. PNsIgA and total IgA in saliva. (**A**) PNsIgA, (**B**) total IgA, and (**C**) PNsIgA/total IgA ratio throughout the course of peanut (purple) or placebo (gold) OIT. Data are shown as mean ± standard error of the mean. *$P < .01$; †$P < .05$.

remission group on average remained constant even off therapy, whereas the other groups had a trend toward a rapid decrease off treatment. Overall, PnOIT causes large increases in salivary PNsIgG4, but was not predictive of clinical outcome.

Salivary IgA during PnOIT treatment and avoidance

The PNsIgA increased in participants treated with PnOIT and reached a plateau by week 30. The PNsIgA was significantly higher in the PnOIT group than in the placebo group at week 30 (Figure 3, *A*). Total IgA was similar between placebo and PnOIT groups with both increasing over time (Figure 3, *B*). When PNsIgA was normalized to total IgA, the ratio of PNsIgA to total IgA increased sharply in the PnOIT group by week 30 and gradually declined thereafter, whereas only small changes were observed in the placebo group (Figure 3, *C*).

When stratified by clinical outcome within the PnOIT group, the not desensitized/no remission group had significantly higher salivary PNsIgA at baseline compared with the desensitized/remission group (Figure 4, *A*). The same held true for total IgA (Figure 4, *B*). When we normalized PNsIgA to total IgA, there was a similar trend as observed for PNsIgA (Figure 4, *C*). There is also a trend for PNsIgA and total IgA in the not desensitized/no remission group at weeks 134 and 160 with higher levels noted when compared with both desensitized groups.

Correlations between salivary and serum immunoglobulin responses

To investigate local versus systemic responses, we compared salivary PNsIgG4 to serum PNsIgG4. Correlation plots were produced for each time point, and statistically significant correlations were identified ($P < .0001$ for all time points; Figure 5). These results indicate a high correlation between local and systemic PNsIgG4 production. In contrast, serum PNsIgA was below the limit of detection for greater than 80% of samples during treatment and avoidance and, therefore, could not be correlated with salivary PNsIgA.

DISCUSSION

To investigate the effects of PnOIT on salivary immunoglobulins, we utilized saliva samples collected from the ITN IMPACT trial. Compared with the placebo group, the PnOIT group had significantly increased PNsIgG4 throughout the course of therapy, indicating a relationship between peanut exposure and production of PNsIgG4. There were similar levels of total IgG4 in the placebo and PnOIT groups, which was not surprising, because PnOIT only modulates the peanut-specific immune response. However, the increase in salivary IgG4 over

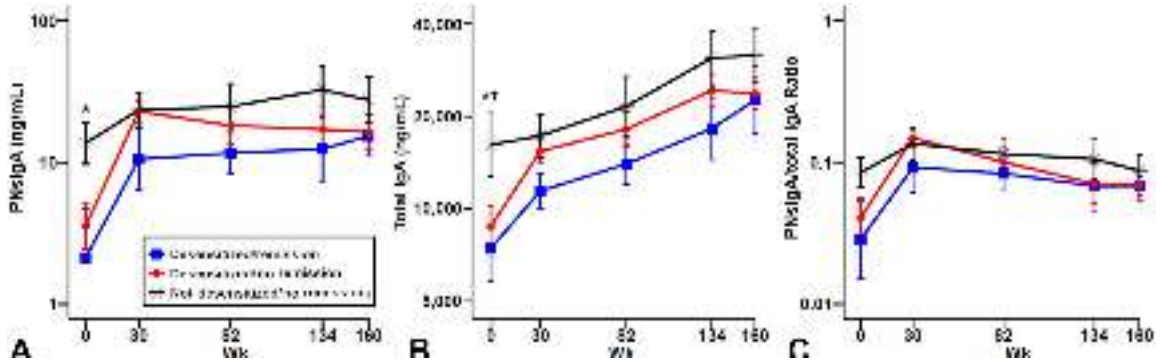

FIGURE 4. PNsIgA and total IgA in saliva by clinical outcome. (**A**) PNsIgA, (**B**) total IgA, and (**C**) PNsIgA/total IgA ratio in desensitized/remission (blue), desensitized/no remission (red), and not desensitized/no remission (black) OIT participants. Data are shown as mean ± standard error of the mean. *$P < .05$ for desensitized/remission versus not desensitized/no remission; †$P < .05$ for desensitized/no remission versus not desensitized/no remission.

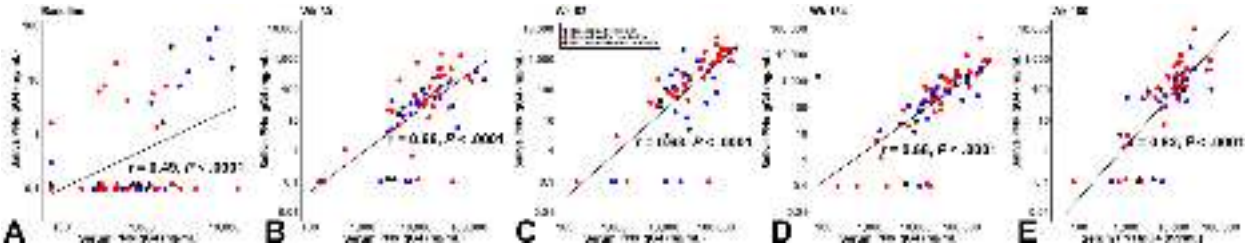

FIGURE 5. Correlations between salivary and serum PNsIgG4. Correlations in the PnOIT group at (**A**) week 0, (**B**) week 30, (**C**) week 82, (**D**) week 134, and (**E**) week 160. Lines represent linear regression lines and gray bands represent the 95% confidence intervals around the regression lines.

time was unexpected and may be due to the developing immune system in these young children.

The PnOIT group had a sharp increase in PNsIgA by 30 weeks compared with the placebo group. These findings indicate a pronounced effect by PnOIT to enhance PNsIgA production at the oral mucosal surface. Daily administration of peanut antigen drives PNsIgA during build-up (weeks 0−30) and plateaus thereafter, indicating a maximum threshold for antigen-specific IgA production. Interestingly, serum PNsIgA was not detectable in the vast majority of subjects, indicating a more robust local response to orally administered peanut antigen. One interpretation of this finding is that salivary PNsIgA may play a role in the desensitization and remission mechanisms of PnOIT and may reflect the amount of PNsIgA present at the gastrointestinal mucosal surface, as was shown in a mouse model with ovalbumin.[18] Furthermore, mucosal IgA is responsible for immune exclusion,[19] and in the context of PnOIT, may prevent peanut from being absorbed systemically. Further mechanistic studies are warranted to determine the role of mucosal IgA following OIT.

The ITN IMPACT trial had well-defined end points for desensitization and remission based on DBPCFC outcomes at weeks 134 and 160. By using samples from this trial, we hypothesized that there would be distinct characteristics in the remission group. Contrary to what we expected, the desensitized/remission group did not have significantly higher salivary PNsIgG4 or PNsIgA than the other OIT outcome groups. In fact, the not desensitized/no remission group had significantly higher salivary PNsIgA at baseline. This surprising data suggests that the sharp increase from weeks 0 to 30 is associated with desensitization and that the increase in the response rather than the quantity of the response is indicative of desensitization. Of note, a previous study examined salivary IgA after peanut sublingual immunotherapy and similarly found the increase in PNsIgA was correlated with increasing amounts of peanut protein tolerated during DBPCFC.[20] One possible interpretation of these results is that high levels of mucosal IgA may sequester the peanut antigen, preventing uptake by tolerogenic dendritic cells that are responsible for tolerance induction. Alternatively, the significantly higher PNsIgA in the not desensitized/no remission group at baseline may be an indicator of inflammation, which may limit successful outcomes on OIT.[21] Therefore, high levels of mucosal IgA at baseline may not be advantageous and, instead, may indicate a decreased likelihood of tolerance induction.

The clinical implications of this work are 2-fold: predicting which participants may respond positively to PnOIT and monitoring outcomes throughout the course of therapy. Currently, there are no accepted assays available to predict participant-specific responses to OIT, although thresholds for baseline PNsIgE in serum may be informative.[9,22] Monitoring OIT is also challenging owing to lack of predictive biomarkers. Direct basophil activation testing has emerged as a potential assay to monitor OIT,[22,23] although these types of assays are technically difficult and require whole blood that needs to be processed

quickly. Indirect basophil activation testing has recently been reported to have high diagnostic accuracy[24]; however, it has not been tested in monitoring OIT outcomes. Alternatively, saliva is easily accessible and noninvasive and can be stored frozen for later analysis. Here, although the sample size of groups stratified by clinical outcome was relatively small, we demonstrated that high levels of PNsIgA in saliva at baseline may indicate decreased likelihood of desensitization, which would be an impactful predictor if validated in other larger trials. Similarly, increases in PNsIgA within 30 weeks of starting OIT may be utilized to monitor successful outcomes.

In conclusion, we demonstrated that PnOIT has a substantial effect on PNsIgA and PNsIgG4 in saliva compared with placebo treatment. These data give insight into mucosal responses induced by PnOIT and suggest a role for mucosal IgA and IgG4 in PnOIT-induced treatment outcomes. It is noteworthy that, when therapy was discontinued, PNsIgG4 decreased sharply, whereas PNsIgA remained elevated. Importantly, both PNsIgG4 and PNsIgA remain higher than baseline levels even when therapy was discontinued. Because saliva is easily obtained, biomarkers within this sample type may provide further mechanistic insights as well as prove useful for monitoring clinical outcomes.

REFERENCES

1. Lieberman JA, Gupta RS, Knibb RC, Haselkorn T, Tilles S, Mack DP, et al. The global burden of illness of peanut allergy: a comprehensive literature review. Allergy 2021;76:1367-84.
2. Jones SM, Pons L, Roberts JL, Scurlock AM, Perry TT, Kulis M, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. J Allergy Clin Immunol 2009;124:292-300.e1-97.
3. Vickery BP, Pons L, Kulis M, Steele P, Jones SM, Burks AW. Individualized IgE-based dosing of egg oral immunotherapy and the development of tolerance. Ann Allergy Asthma Immunol 2010;105:444-50.
4. PALISADE Group of Clinical Investigators, Vickery BP, Vereda A, Casale TB, Beyer K, du Toit G, et al. AR101 oOral immunotherapy for peanut allergy. N Engl J Med 2018;379:1991-2001.
5. Smeekens JM, Kulis MD. Evolution of immune responses in food immunotherapy. Immunol Allergy Clin North Am 2020;40:87-95.
6. Patil SU, Ogunniyi AO, Calatroni A, Tadigotla VR, Ruiter B, Ma A, et al. Peanut oral immunotherapy transiently expands circulating Ara h 2-specific B cells with a homologous repertoire in unrelated subjects. J Allergy Clin Immunol 2015;136:125-134.e12.
7. Burton OT, Logsdon SL, Zhou JS, Medina-Tamayo J, Abdel-Gadir A, Noval Rivas M, et al. Oral immunotherapy induces IgG antibodies that act through FcgammaRIIb to suppress IgE-mediated hypersensitivity. J Allergy Clin Immunol 2014;134:1310-1317.e6.
8. Varshney P, Jones SM, Scurlock AM, Perry TT, Kemper A, Steele P, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. J Allergy Clin Immunol 2011;127:654-60.
9. Vickery BP, Scurlock AM, Kulis M, Steele PH, Kamilaris J, Berglund JP, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. J Allergy Clin Immunol 2014;133:468-75.
10. Wood RA. Food allergen immunotherapy: current status and prospects for the future. J Allergy Clin Immunol 2016;137:973-82.
11. Tordesillas L, Berin MC. Mechanisms of oral tolerance. Clin Rev Allergy Immunol 2018;55:107-17.
12. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med 2015;372:803-13.
13. Konstantinou GN, Nowak-Wegrzyn A, Bencharitiwong R, Bardina L, Sicherer SH, Sampson HA. Egg-white-specific IgA and IgA2 antibodies in egg-allergic children: is there a role in tolerance induction? Pediatr Allergy Immunol 2014;25:64-70.
14. Orgel K, Burk C, Smeekens J, Suber J, Hardy L, Guo R, et al. Blocking antibodies induced by peanut oral and sublingual immunotherapy suppress basophil activation and are associated with sustained unresponsiveness. Clin Exp Allergy 2019;49:461-70.
15. Santos AF, James LK, Bahnson HT, Shamji MH, Couto-Francisco NC, Islam S, et al. IgG4 inhibits peanut-induced basophil and mast cell activation in peanut-tolerant children sensitized to peanut major allergens. J Allergy Clin Immunol 2015;135:1249-56.
16. Jones SM, Kim EH, Nadeau KC, Nowak-Wegrzyn A, Wood RA, Sampson HA, et al. Efficacy and safety of oral immunotherapy in children aged 1−3 years with peanut allergy (the Immune Tolerance Network IMPACT trial): a randomised placebo-controlled study. Lancet 2022;399:359-71.
17. Bednar KJ, Hardy L, Smeekens J, Raghuwanshi D, Duan S, Kulis MD, et al. Antigenic liposomes for generation of disease-specific antibodies. J Vis Exp 2018;140:58285.
18. Externest D, Meckelein B, Schmidt MA, Frey A. Correlations between antibody immune responses at different mucosal effector sites are controlled by antigen type and dosage. Infect Immun 2000;68:3830-9.
19. Zhang B, Liu E, Gertie JA, Joseph J, Xu L, Pinker EY, et al. Divergent T follicular helper cell requirement for IgA and IgE production to peanut during allergic sensitization. Sci Immunol 2020;5:eaay2754.
20. Kulis M, Saba K, Kim EH, Bird JA, Kamilaris N, Vickery BP, et al. Increased peanut-specific IgA levels in saliva correlate with food challenge outcomes after peanut sublingual immunotherapy. J Allergy Clin Immunol 2012;129:1159-62.
21. Hansen IS, Baeten DLP, den Dunnen J. The inflammatory function of human IgA. Cell Mol Life Sci 2019;76:1041-55.
22. Tsai M, Mukai K, Chinthrajah RS, Nadeau KC, Galli SJ. Sustained successful peanut oral immunotherapy associated with low basophil activation and peanut-specific IgE. J Allergy Clin Immunol 2020;145:885-896.e6.
23. Patil SU, Steinbrecher J, Calatroni A, Smith N, Ma A, Ruiter B, et al. Early decrease in basophil sensitivity to Ara h 2 precedes sustained unresponsiveness after peanut oral immunotherapy. J Allergy Clin Immunol 2019;144:1310-1319.e4.
24. Ruinemans-Koerts J, Brouwer ML, Schmidt-Hieltjes Y, Stevens P, Merkus P, Doggen CMJ, et al. The indirect basophil activation test is a safe, reliable, and accessible tool to diagnose a peanut allergy in children. J Allergy Clin Immunol Pract 2022;10:1305-1311.e3.