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

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Abstract

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 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 to <48 months at screening, were enrolled and randomized to peanut or placebo 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, 30, 82, 134, and 160 weeks to quantify peanut-specific and total IgG4 and IgA.

Results: Participants who received PnOIT experienced significant increases in peanut-specific IgG4 in saliva, whereas participants on placebo did not ($p<0.01$ at all time points). Peanut-specific IgA/total IgA ratio was also significantly increased in participants treated with PnOIT when compared to those receiving placebo at 30 and 82 weeks ($p<0.05$). During PnOIT, desensitized participants had increased peanut-specific IgA that plateaued, whereas the not desensitized/no remission group did not change over time. Interestingly, when the PnOIT group was evaluated by clinical outcome, peanut-specific IgA was higher at baseline in the not desensitized/no remission group compared to the desensitized/remission group ($p<0.05$).

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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.

Keywords

peanut allergy; oral immunotherapy; IgA; IgG4; saliva

Introduction

Peanut allergy is a growing public health concern affecting 2% of the US population.(1) The current standard of care is 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, one PnOIT product, Palforzia, recently gained 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 IgG4 in plasma increases sharply within the first few months with some studies also showing increases in peanut-specific IgA throughout therapy.(6, 7) Peanut-specific IgE increases for the first 6 months on OIT, and then decreases below baseline levels after ~12 months.(8, 9) While these changes are consistently observed with treatment, they have had little success when used as biomarkers to predict OIT outcomes.(10) However, since 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 non-allergic individuals that typically results in elevated levels of serum antigen-specific IgG4 and IgA. (11) For example, in the LEAP trial, early introduction of peanut in infants that were protected from peanut allergy resulted in substantial increases in peanut-specific IgG4, 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 that 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) While 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 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 to <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 that completed the protocol (i.e. 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 1). To assess the immunologic response to PnOIT at the oral mucosal surface and its potential to predict treatment outcomes, we aimed to quantify salivary peanut-specific and total IgG4 and IgA in the IMPACT trial and compare these to their sera counterparts.

Methods:

Clinical trial description

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

Saliva samples

Saliva was collected either by suction with a syringe or spitting directly into a cryovial after first rinsing 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 ELISAs

For peanut-specific and total IgG4 ELISAs, 96-well plates were coated with 2 μg/mL of anti-human 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% BSA in PBS with 0.05% Tween 20. Saliva samples were diluted 1:10 for peanut-specific and 1:20 for total IgG4. Standard curves were generated with native human IgG4 protein (Abcam, Cambridge, MA) ranging from 0.24–250 ng/mL. Samples and standards were detected with a 1:1000 dilution of anti-human IgG4 Fc-HRP (clone HP6025, Southern Biotech, Birmingham, AL). 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).

For peanut-specific and total IgA ELISAs, 96-well plates were coated with 2 μg/mL of anti-human 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% BSA in PBS with 0.05% Tween 20. Saliva samples were diluted 1:50 for peanut-specific and 1:20,000 for total IgA. Standard curves were generated with purified human IgA (Bethyl Labs, Montgomery, TX) ranging from 0.6–60 ng/mL. Samples were detected with a 1:1000 dilution of anti-human 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 avoidance phase and had an evaluable blinded DBPCFC at the end of the maintenance and avoidance phases (per protocol population for the secondary endpoint). 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 $p<0.05$ (two-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, 30, 82, 134, and 160 weeks for quantification of salivary peanut-specific and total IgG4, and serum peanut-specific IgG4 (PNsIgG4). Participants receiving PnOIT demonstrated significant increases in PNsIgG4 in saliva, whereas participants receiving placebo did not (placebo vs. PnOIT, $p<0.01$ at all time points; Figure 1A). 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 1B). 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 1C). PNsIgG4 to total IgG4 ratio did not increase in the placebo group during the trial.

For the 69 participants that completed the protocol, when stratified by clinical outcome, a significant difference was noted in PNsIgG4 between the desensitized/remission and desensitized/no remission groups at week 82 (Figure 2A). For total IgG4, the not desensitized/no remission group trended towards 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 desensitized/no remission groups at week 160 (Figure 2B). 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 to the other groups where, on average, there was an increase at week 30 and remained elevated throughout treatment at week 134 (Figure 2C). Interestingly, the desensitized/remission group on average remained constant even off therapy, while the other groups had a trend towards 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

Peanut-specific IgA (PNsIgA) increased in participants treated with PnOIT and reached a plateau by week 30. PNsIgA was significantly higher in the PnOIT group compared to the placebo group at week 30 (Figure 3A). Total IgA was similar between placebo and PnOIT groups with both increasing over time (Figure 3B). When peanut-specific IgA was

normalized to total IgA, the ratio of peanut-specific IgA 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 3C).

When stratified by clinical outcome within the PnOIT group, the not desensitized/no remission group had significantly higher salivary PNsIgA at baseline compared to the desensitized/remission group (Figure 4A). The same held true for total IgA (Figure 4B). When we normalized PNsIgA to total IgA, there was a similar trend as observed for PNsIgA (Figure 4C). 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 to 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 ($p<0.0001$ 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 >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 to 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, since PnOIT only modulates the peanut-specific immune response. However, the increase in salivary IgG4 over 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 to 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 GI mucosal surface, as was shown in a mouse model with OVA. (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 IMPACT trial had well-defined endpoints 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 are 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 SLIT and similarly found the increase in peanut IgA 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 twofold: 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 peanut-specific IgE in serum may be informative. (9, 22) Monitoring OIT is also challenging due 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, non-invasive, 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 peanut-specific IgA and IgG4 in saliva when compared to 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, while PNsIgA remained elevated. Importantly, both PNsIgG4 and PNsIgA remain higher than baseline levels even when therapy was discontinued. Since saliva is easily obtained, biomarkers within this sample type may provide further mechanistic insights as well as prove useful for monitoring clinical outcomes.

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Abbreviations:

DBPCFC	Double-blind placebo-controlled food challenge
OIT	Oral immunotherapy
PnOIT	Peanut oral immunotherapy
PNsIgA	Peanut-specific IgA
PNsIgG4	Peanut-specific IgG4

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Highlights

What is already known about this topic?

Serum peanut-specific IgG4 and IgA are significantly increased after peanut OIT, 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?

PnOIT 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 OIT is beneficial for desensitization.

How does this study impact current management guidelines?

These data provide insight into OIT-induced mucosal responses and suggest utility of these easily obtained samples for biomarker development.

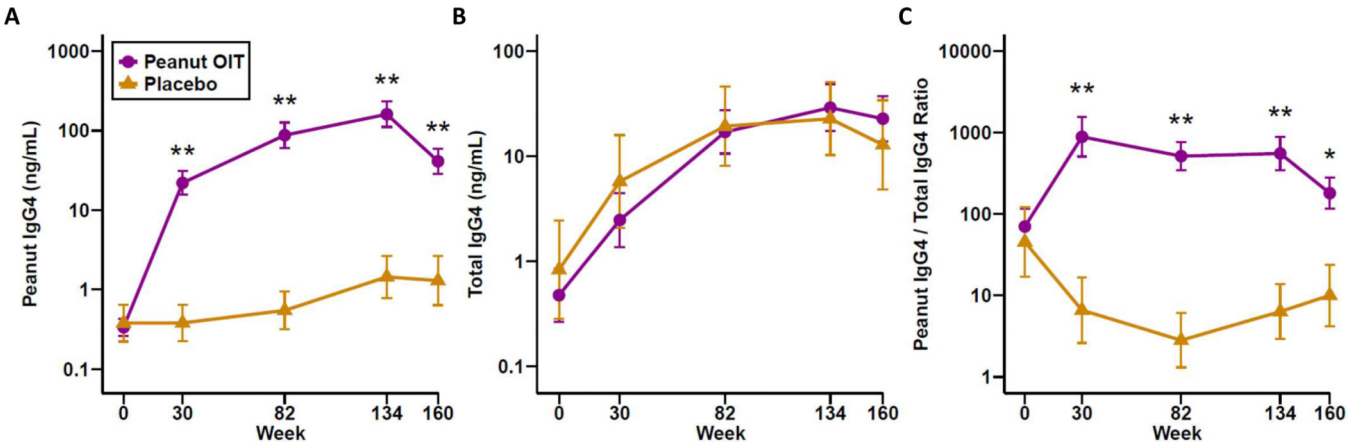

Figure 1.

Peanut-specific and total IgG4 in saliva. Peanut-specific IgG4 (A), total IgG4 (B), and peanut IgG4/total IgG4 ratio (C) throughout the course of peanut (purple) or placebo (gold) OIT. Data are show as means ± standard error of the mean (SEM). *P<0.05, **P<0.01.

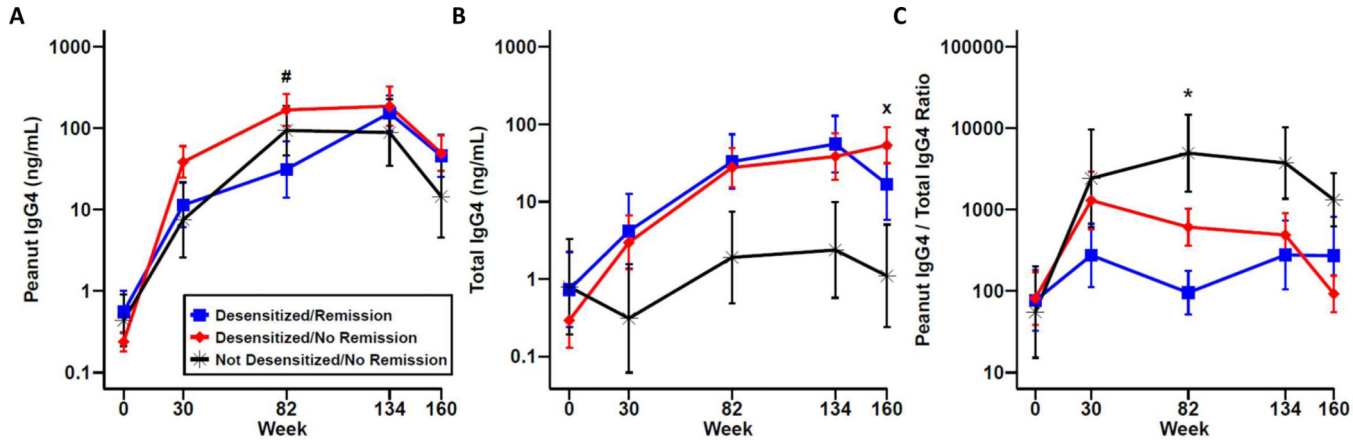

Figure 2.

Peanut-specific and total IgG4 in saliva by clinical outcome. Peanut-specific IgG4 (A), total IgG4 (B), and peanut IgG4/total IgG4 ratio (C) in desensitized/remission (blue), desensitized/no remission (red), and not desensitized/no remission (black) OIT participants. Data are show as mean ± standard error of the mean (SEM). # $P<0.05$ for desensitized/remission vs desensitized/no remission; x $P<0.05$ for desensitized/no remission vs not desensitized/no remission; * $P<0.05$ for desensitized/remission vs not desensitized/no remission.

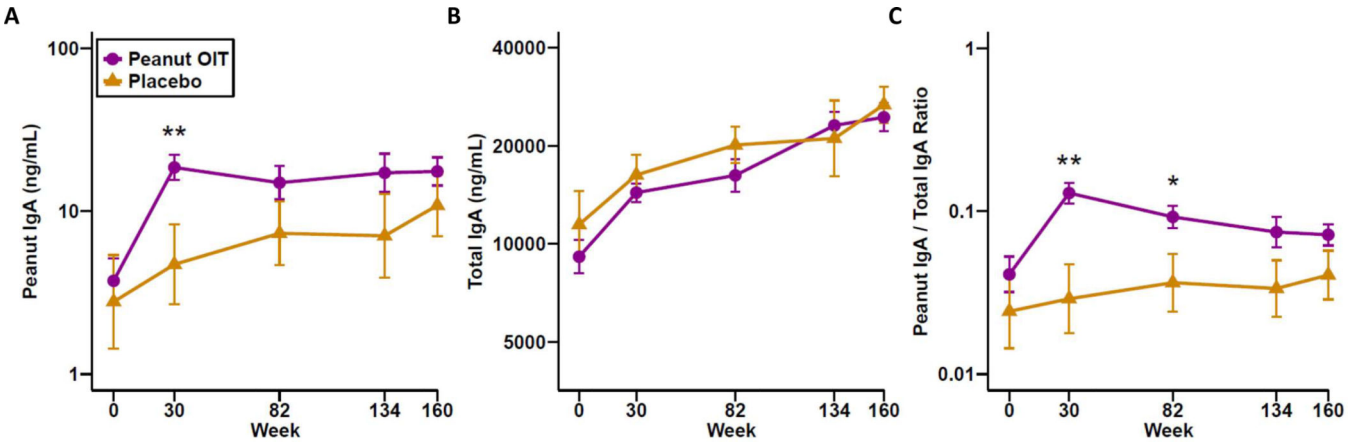

Figure 3.

Peanut-specific and total IgA in saliva. Peanut-specific IgA (A), total IgA (B), and peanut IgA/total IgA ratio (C) throughout the course of peanut (purple) or placebo (gold) OIT. Data are show as means ± standard error of the mean (SEM). *P<0.05, **P<0.01.

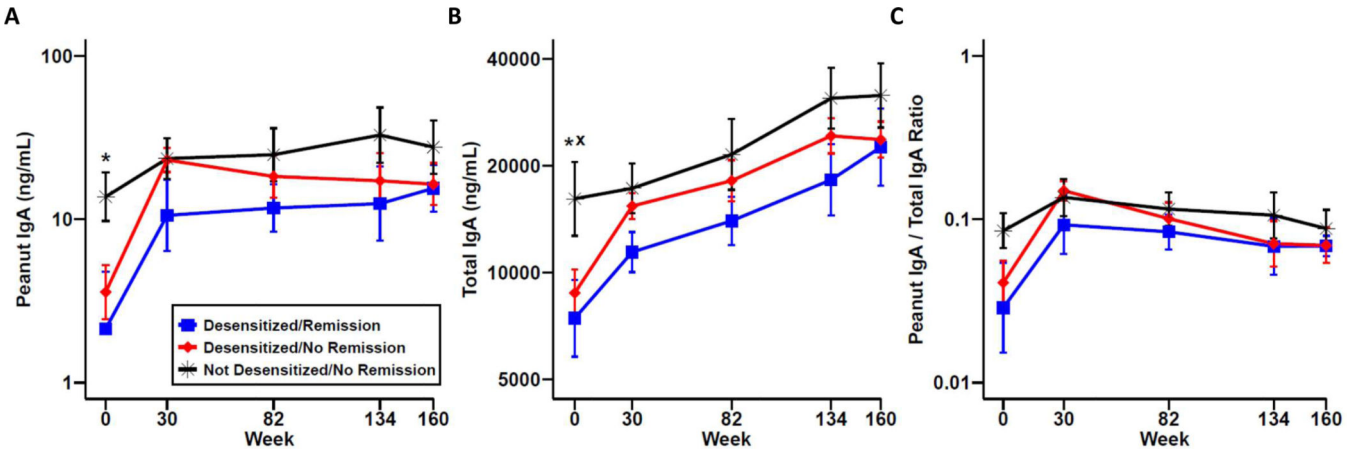

Figure 4.

Peanut-specific and total IgA in saliva by clinical outcome. Peanut-specific IgA (A), total IgA (B), and peanut IgA/total IgA ratio (C) in desensitized/remission (blue), desensitized/no remission (red), and not desensitized/no remission (black) OIT participants. Data are show as mean ± standard error of the mean (SEM). x $P<0.05$ for desensitized/no remission vs not desensitized/no remission; * $P<0.05$ for desensitized/remission vs not desensitized/no remission.

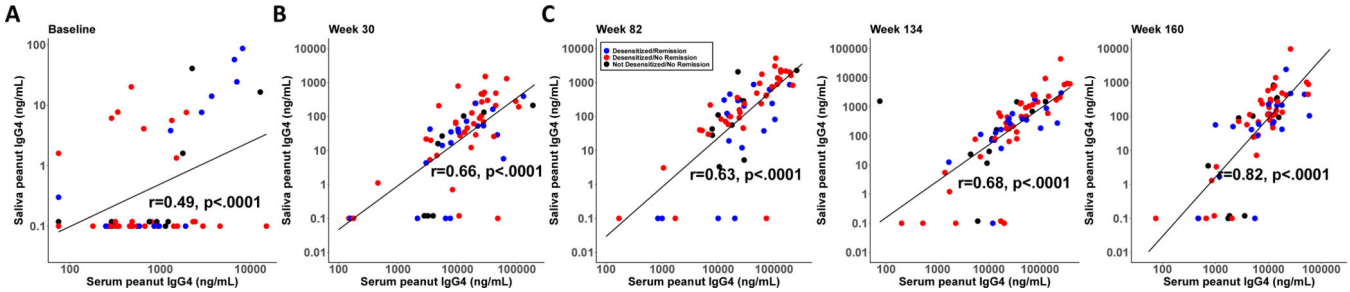

Figure 5.

Correlations between salivary and serum peanut-specific IgG4. Correlations in the PnOIT group at weeks 0 (A), 30 (B), 82 (C), 134 (D), and 160 (E). Lines represent linear regression lines and gray bands represent the 95% confidence intervals around regression lines.

Table 1.

Demographics of subjects on PnOIT.

	Desensitized / Remission (n=19)	Desensitized / No Remission (n=40)	Not Desensitized / No Remission (n=10)
Age (Months)	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%)
Peanut-specific IgE (serum)	16.5 (10.38–46.5)	69.5 (38–196.75)	135.4 (50.5–316.75)
Total IgE (serum)	486 (192.5–703.75)	400.5 (192.5–617.75)	452 (247.25–772.5)

*Data are n (%) or median (IQR)