REVIEW

Art v 3 sensitization is associated with increased immunological complexity but not clinical severity in lipid transfer protein syndrome

Art v 3 and severity in LTP syndrome

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KEY WORDS

Lipid transfer protein; Art v 3; food allergy; IgE; profilin; cofactors; anaphylaxis.

Impact statement

Identification of Art v 3 sensitization as a marker of severity improves risk stratification in LTP syndrome, highlighting a high-risk phenotype driven by cofactors and supporting personalized clinical management strategies.

Summary

Background. Lipid transfer protein (LTP)–mediated food allergy represents one of the most severe and heterogeneous forms of IgE-mediated food allergy in Mediterranean populations. Although Pru p 3 is the main marker of LTP sensitization, the clinical relevance of pollen-derived LTPs such as Art v 3 remains incompletely defined. **Methods.** We conducted a retrospective observational study including 241 adult patients with LTP-mediated food allergy and confirmed sensitization to Pru p 3. Art v 3–specific IgE was determined using component-resolved diagnostics. Clinical severity was assessed using the Food Allergy Severity Score (FASS). Profilin sensitization was analyzed when available. Correlations were evaluated using Spearman's coefficient. **Results.** Art v 3 sensitization was detected in 124 patients (51.5%). A higher proportion of moderate-to-severe reactions (FASS ≥ 3) was observed in Art v 3–sensitized patients compared with non-sensitized patients (64.0% vs 56.3%), although this difference did not reach statistical significance (OR = 1.38; 95% CI: 0.82–2.31). A statistically significant but low positive correlation was observed between Art v 3– and Pru p 3–specific IgE levels (Spearman's ρ = 0.46). Profilin sensitization was not associated with clinical severity (p = 0.36). **Conclusions.** Art v 3 sensitization is associated with a more complex immunological profile rather than acting as an independent predictor of clinical severity. Its clinical value may lie in risk stratification. Prospective studies are needed.

INTRODUCTION

Lipid transfer protein (LTP)–mediated food allergy represents one of the most relevant and complex models of IgE-mediated food allergy in Mediterranean populations, characterized by marked clinical heterogeneity and a significant risk of severe systemic reactions (1–3).

Pru p 3, the major peach LTP, has traditionally been considered the main marker of LTP sensitization and the central driver of cross-reactivity among plant-derived foods (4–6). However, advances in component-resolved diagnostics have identified additional molecules that may contribute to the clinical expression of LTP syndrome, including Art v 3, the LTP from *Artemisia vulgaris* pollen.

The clinical presentation of LTP syndrome is highly variable, ranging from mild oral symptoms to severe anaphylaxis. This variability is influenced by multiple factors, including cofactors such as physical exercise, non-steroidal anti-inflammatory drugs (NSAIDs), and alcohol consumption, as well as the individual molecular sensitization profile (7–9).

Recent studies suggest that sensitization to multiple LTPs may be associated with an expansion of the IgE repertoire and a higher risk of severe reactions. In this context, Art v 3 sensitization has been proposed as a potential marker of increased clinical severity, although available evidence remains limited and sometimes inconsistent.

Additionally, sensitization to other panallergens, such as PR-10 proteins and profilins, has been associated with a milder clinical phenotype in some populations, further highlighting the complexity of the immunological landscape in LTP syndrome.

The aim of this study was to evaluate the association between Art v 3 sensitization and clinical severity in a large cohort of patients with LTP-mediated food allergy, as well as its relationship with immunological parameters, cofactors, and profilin sensitization.

METHODS

Study design

A retrospective, observational study was conducted in a cohort of adult patients diagnosed with lipid transfer protein (LTP)–mediated food allergy, consecutively evaluated in a specialized Allergy Unit over an extended period of clinical follow-up.

Study population

Patients were included if they met the following criteria:

- clinical history compatible with IgE-mediated food allergy
- confirmed sensitization to Pru p 3
- availability of specific IgE measurements to Art v 3

All patients included in the study had available measurements of both Pru p 3 and Art v 3–specific IgE as part of routine component-resolved diagnostics, minimizing potential selection bias.

Patients with non–IgE-mediated food reactions or incomplete clinical data were excluded.

Clinical and demographic variables

The following variables were systematically collected:

- age and sex
- foods implicated in allergic reactions
- type of clinical symptoms (oral, cutaneous, gastrointestinal, respiratory, and cardiovascular)
- history of anaphylaxis
- number of foods involved throughout the clinical course

Assessment of clinical severity

The severity of food allergic reactions was classified using the Food Allergy Severity Score (FASS), a validated tool that allows objective stratification of clinical severity.

Reactions were categorized according to FASS score, with particular attention to:

- FASS ≥ 3, considered indicative of moderate-to-severe systemic reactions
- presence of anaphylaxis, defined according to international criteria

Clinical cofactors

The presence of cofactors associated with allergic reactions was evaluated. Cofactors were defined as concurrent circumstances capable of lowering the reaction threshold or increasing reaction severity. Specifically, the following were considered:

- physical exercise
- intake of non-steroidal anti-inflammatory drugs (NSAIDs)
- alcohol consumption

Patients were classified according to the presence or absence of cofactors during documented allergic reactions.

Immunological assessment

Specific IgE determinations were performed using standardized immunoassay techniques (ImmunoCAP®, Thermo Fisher Scientific).

The following parameters were analyzed:

- specific IgE to Pru p 3
- specific IgE to Art v 3
- total serum IgE

Sensitization to Art v 3 was defined as specific IgE > 0.35 kU/L, in accordance with standard clinical practice. Patients were classified as Art v 3–sensitized or non-sensitized based on this threshold.

Profilin sensitization

Sensitization to profilin was recorded when available and included as a binary variable (positive vs negative), defined according to standard diagnostic criteria.

Statistical analysis

Quantitative variables were described using mean ± standard deviation or median and interquartile range, depending on data distribution. Qualitative variables were expressed as frequencies and percentages.

Group comparisons were performed using:

- Mann–Whitney U test for continuous variables
- chi-square test or Fisher's exact test for categorical variables

Correlations between Art v 3– and Pru p 3–specific IgE levels were evaluated using Spearman's correlation coefficient. Correlation strength was interpreted according to predefined thresholds.

The association between Art v 3 sensitization and clinical severity (FASS ≥ 3) was assessed by calculating odds ratios (OR) with 95% confidence intervals (CI).

A p-value < 0.05 was considered statistically significant.

Missing data
No relevant missing data were identified for the main clinical and immunological variables included in the analysis. Only patients with complete information required for severity classification and IgE determination were included in the final cohort.

RESULTS

Cohort characteristics

A total of 241 adult patients with LTP-mediated food allergy and confirmed sensitization to Pru p 3 were included in the study. Among them, 124 patients (51.5%) were sensitized to Art v 3, while 117 (48.5%) were non-sensitized.

Baseline characteristics of the study population are summarized in **Table 1**. Patients sensitized to Art v 3 showed significantly higher total IgE and Pru p 3–specific IgE levels compared with non-sensitized patients. No significant differences were observed between groups in age, sex distribution, or prevalence of cofactors.

Values are presented as mean ± standard deviation (SD), median (interquartile range, IQR), or number (percentage), as appropriate.

FASS: Food Allergy Severity Score; IgE: immunoglobulin E; NS: not statistically significant ($p \geq 0.05$).

Art v 3 sensitization was defined as specific IgE > 0.35 kU/L. Cofactors included physical exercise, non-steroidal anti-inflammatory drugs (NSAIDs), and alcohol consumption.

Profilin sensitization was analyzed as a binary variable (positive vs negative).

Clinical severity

The proportion of moderate-to-severe reactions (FASS ≥ 3) was higher in Art v 3–sensitized patients compared with non-sensitized patients (64.0% vs 56.3%). However, this difference did not reach statistical significance (OR = 1.38; 95% CI: 0.82–2.31).

The distribution of clinical severity according to Art v 3 sensitization is shown in **Figure 2**.

Influence of cofactors

The prevalence of cofactors was similar between groups (15.2% in Art v 3–sensitized vs 14.3% in non-sensitized patients), as shown in **Table 1**.

When stratified by the presence of cofactors, patients sensitized to Art v 3 showed higher FASS scores compared with those without cofactors. The interaction between Art v 3 sensitization and cofactors is illustrated in **Figure 3**, showing a non-significant trend toward increased clinical severity.

Correlation analysis

Correlation analysis revealed a statistically significant but low positive correlation between Art v 3– and Pru p 3–specific IgE levels (Spearman's ρ = 0.46), as shown in **Figure 4**.

Profilin sensitization

Profilin sensitization was observed in a small proportion of patients. No significant association was found between profilin sensitization and clinical severity (p = 0.36). Additionally, no association was observed between profilin sensitization and Art v 3 sensitization.

Summary of findings
Overall, patients sensitized to Art v 3 exhibited a more complex immunological profile, characterized by higher total IgE and Pru p 3–specific IgE levels. No significant differences were observed in clinical severity, prevalence of cofactors, or profilin sensitization between groups.

DISCUSSION

The present study provides an integrated clinical and immunological characterization of lipid transfer protein (LTP) syndrome, focusing on the role of Art v 3 sensitization. Our findings indicate that Art v 3 sensitization is associated with a more complex immunological profile, reflected by higher total IgE and Pru p 3–specific IgE levels, but not with a statistically significant increase in clinical severity.

Although a higher proportion of moderate-to-severe reactions was observed among Art v 3–sensitized patients, this difference did not reach statistical significance. This finding suggests that Art v 3 sensitization alone is not an independent predictor of severe reactions, but rather may be associated with underlying immunological mechanisms contributing to disease expression.

The correlation between Art v 3– and Pru p 3–specific IgE levels was statistically significant but of low magnitude (Spearman's ρ = 0.46), indicating only partial overlap between both sensitization patterns. This finding supports the hypothesis that Art v 3 sensitization may reflect a partially independent immunological pathway rather than acting solely as a surrogate marker of Pru p 3 sensitization.

Importantly, patients sensitized to Art v 3 exhibited higher levels of total IgE and Pru p 3–specific IgE, suggesting an expansion of the IgE repertoire. Previous studies have demonstrated that sensitization to multiple LTP molecules is associated with an increased risk of severe reactions (17). In this context, Art v 3 sensitization may be better interpreted as a marker of broader molecular sensitization rather than a direct determinant of clinical severity.

The role of cofactors in LTP-mediated food allergy is well established (5,13). However, in our study, the prevalence of cofactors was similar between groups, indicating that baseline exposure to cofactors does not explain the observed differences in clinical expression. Nevertheless, the interaction between Art v 3 sensitization and cofactors, as illustrated in Figure 3, suggests that both factors may contribute synergistically to modulating clinical severity, although this observation should be interpreted with caution.

Sensitization to profilin was not associated with clinical severity in our cohort. Although previous studies have suggested a potential protective role of panallergens such as profilins and PR-10 proteins (18), this effect was not observed in our data. This discrepancy may be

explained by the relatively small number of profilin-sensitized patients, which may have limited the statistical power to detect such an association. These findings highlight the complexity of the IgE sensitization profile and suggest that the balance between different allergen families may influence clinical expression.

Taken together, our results support the concept that the clinical heterogeneity of LTP syndrome cannot be explained by single molecular sensitizations alone, but rather by the overall composition and breadth of the IgE repertoire. This aligns with emerging evidence from multiplex studies, which emphasize the importance of molecular complexity in determining clinical risk.

Several limitations should be considered. First, the retrospective design limits the ability to establish causal relationships. Second, no multivariable adjustment was performed to control for potential confounders, such as total IgE levels or the number of sensitized LTP molecules, which may have influenced the observed associations. Although the findings are consistent and biologically plausible, future prospective studies including multivariate analyses would be desirable to further validate these results. Third, the use of a dichotomous cut-off for Art v 3 sensitization may not fully capture potential dose–response relationships. Finally, the absence of multiplex allergen profiling prevents a more detailed characterization of the IgE repertoire.

Despite these limitations, this study includes a relatively large and well-characterized cohort and applies a validated severity score (FASS), strengthening the reliability of the findings. The integration of clinical and molecular data provides a relevant contribution to the understanding of LTP syndrome.

These findings highlight the relevance of considering the overall molecular sensitization profile when evaluating patients with LTP syndrome and support the need for further research to better understand its clinical implications.

CONCLUSIONS

Art v 3 sensitization is associated with a more complex immunological profile, characterized by higher total IgE and Pru p 3–specific IgE levels, suggesting an expansion of the IgE repertoire in patients with lipid transfer protein syndrome.

Although a higher proportion of moderate-to-severe reactions was observed in Art v 3–sensitized patients, this association did not reach statistical significance, indicating that Art v 3 sensitization alone is not an independent predictor of clinical severity.

These findings support the concept that the clinical expression of LTP syndrome is determined by a multifactorial interplay, including the breadth of molecular sensitization rather than single allergenic components.

Future prospective studies incorporating multiplex allergen profiling and evaluation of panallergen sensitization are needed to better define the role of Art v 3 in risk stratification.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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AUTHOR CONTRIBUTIONS

A.C.M.: Conceptualization; Methodology; Analysis; Writing.

J.C.Z.: Development of figures, tables, statistics, references, and review assistance

C.N.G.: Data collection.Translation and text revision

S.Z.P.: Data collection. Translation and text revision

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Table 1. Baseline characteristics of the study population according to Art v 3 sensitization

Variable	Art v 3–sensitized (n = 124)	Non–sensitized (n = 117)	p-value
Age (years), mean ± SD	35.8 ± 13.0	33.6 ± 13.3	NS
Female sex, n (%)	38 (30.6%)	29 (24.8%)	NS
Total IgE (kU/L), median (IQR)	171.7 (92.1–408.8)	91.0 (38.7–308.0)	<0.05
Pru p 3–specific IgE (kU/L), median (IQR)	9.05 (4.3–18.4)	2.42 (1.24–6.18)	<0.001
FASS ≥ 3, n (%)	80 (64.0%)	67 (56.3%)	NS
Cofactors present, n (%)	19 (15.2%)	17 (14.5%)	NS
Profilin sensitization, n (%)	11 (8.9%)	10 (8.5%)	NS

Figure 1

Percentage of patients with moderate-to-severe allergic reactions (FASS ≥3) according to Art v 3 sensitization status.

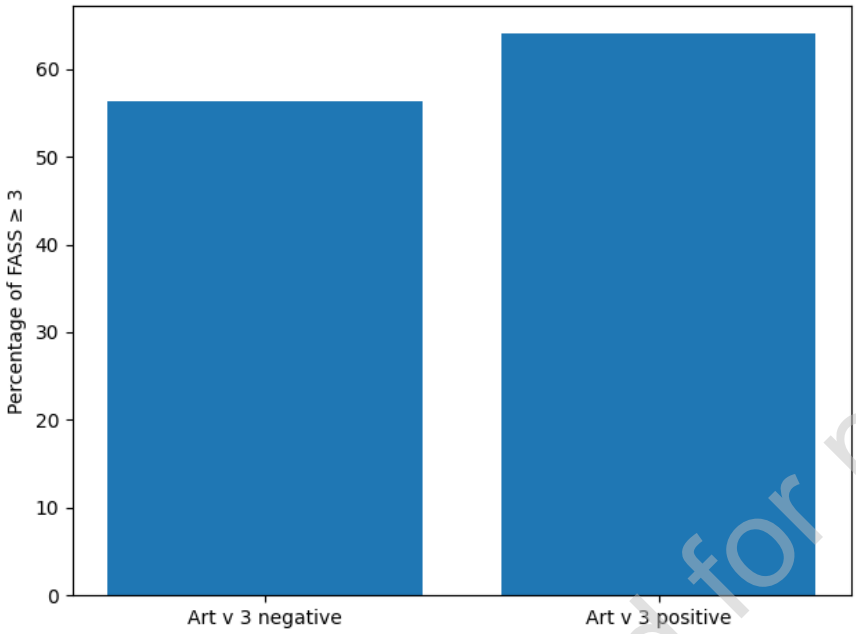

Figure 2

Percentage of patients with moderate-to-severe reactions (FASS ≥3) according to Art v 3 sensitization and presence of clinical cofactors (exercise, NSAIDs, or alcohol).

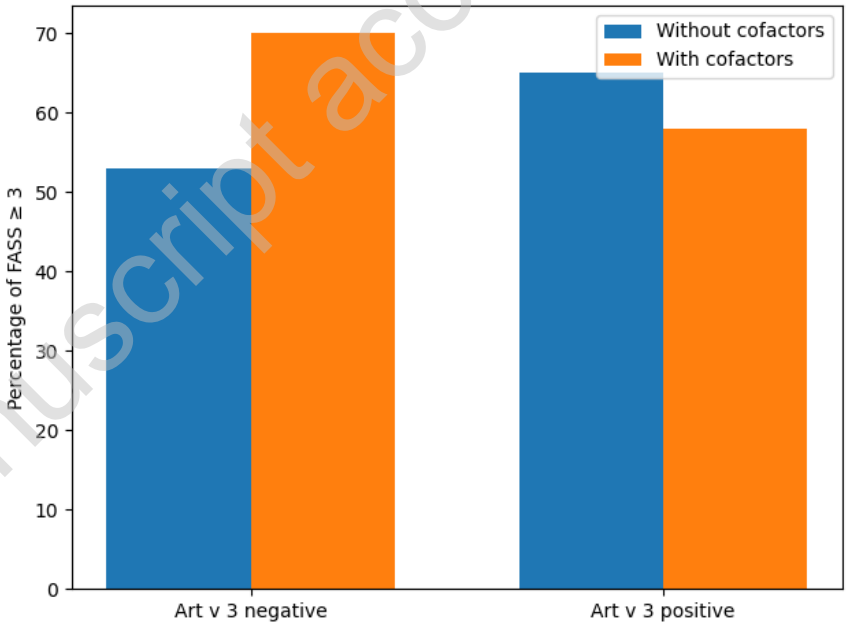

Figure 3

Scatter plot showing the relationship between Art v 3– and Pru p 3–specific IgE levels. A low positive correlation was observed (Spearman's ρ = 0.46).