Abstract

Venom allergy to hymenopteran insects (Hymenoptera venom allergy - HVA) is one of most challenging problems in daily allergology practice. Sting reactions in individuals with HVA result in the development of large local allergic reactions, occurring in adults at a frequency of 2.4-26.4% and in children at a frequency of 11.5-19%, as well as generalized reactions, of which approximately 20% of patients experience life-threatening symptoms. The frequency of systemic reactions following a sting from a hymenopteran insect ranges from 0.3-8.9% in adults and 0.15-0.3% in children. In Europe, bee and wasp venom are the most common causes of severe anaphylaxis in adults (48.2%) and the second most common cause in children (20.2%), with an estimated number of fatal cases ranging from 0.03 to 0.48 per million inhabitants per year.

Venom allergen immunotherapy (VIT) is currently the only effective causal treatment method that restores immunological tolerance in individuals with HVA. This treatment has demonstrated 77-84% efficacy for bee venom allergy, and 91-96% for wasp venom allergy. VIT rapidly reduces the risk of systemic reactions to 2%, and its continuation for 5 years maintains this risk at similar level. Despite the proven clinical efficacy, there is still limited data describing the systemic effects of VIT and its impact on other key pathways and biochemical mechanisms responsible for regulating organism homeostasis, which is not always directly related to the allergic process. Despite significant advancements in diagnostic methods, we are still unable to precisely predict whether long-term and costly VIT will be effective for all patients with HVA.

Metabolomics describes the mutual relationships between metabolites in a given system, proteins (proteomics), RNA (transcriptomics), DNA (genomics), and between them and environmental factors, including allergens. The metabolomic analysis provides a new perspective for identifying non-classical biomarkers of allergic reactions and the influence of VIT on the metabolite profile. As one of the omics sciences, it can also contribute to the development of personalized medicine, including identifying a panel of metabolites to assess the efficacy of VIT.

This study aimed to conduct targeted metabolomic analysis in patients with HVA undergoing VIT and correlate these data with characteristic changes in the immune system associated with this treatment.

The study was conducted in 22 patients with HVA to bee venom, 27 patients with HVA to wasp venom, and 16 individuals in the control group. Throughout the study, patients were evaluated before starting VIT, 24 hours after the first dose, and after 3 months, 1 year, 2 years, and 4-5 years of VIT. Blood samples were collected from study participants, once in the case of the control group and from the patients at each time point. The collected samples underwent complete blood count with differential and targeted metabolomics analysis. A commercial kit allowing the quantification of over 180 metabolites was used. Nonparametric Mann-Whitney U-test and Spearman correlations were used for statistical analysis.

Statistical analysis of the complete blood count results revealed changes in the number of eosinophils, basophils, and monocytes during VIT. Based on metabolomic studies, changes in the concentrations of several amino acids, lipids, acylcarnitines, and biogenic amines were noted. The results showed that patients allergic to wasp or bee venom had a different serum

metabolite profile than individuals in the control group. Furthermore, the serum metabolite profile of patients allergic to wasp venom differs from those allergic to bee venom. VIT led to changes in the serum metabolite levels in both wasp and bee venom allergy treatments.

This study has revealed that metabolomic analysis can reveal new, previously unknown VIT-induced biochemical pathways in HVA patients. In future, the data can help in identifying novel biomarkers that can be used, among others, for prediction of VIT efficacy.