



Letter

Systemic reactions to allergen immunotherapy: A role for measuring a PGD₂ metabolite?

New strategies for predicting and preventing systemic reactions (SRs) to allergen immunotherapy (AIT) may improve the safety profile of this cost-effective therapy.¹ Few studies have measured biological mediators before or during SRs to AIT.^{2–4} Prostaglandin D₂ (PGD₂), which can be detected by measuring one of its metabolites 11- β -prostaglandin F₂- α (11-BPG), may be an important mediator for patients who experience an SR to AIT.⁵ To further understand the potential role for PGD₂ in AIT SRs, we performed 2 pilot studies.

The objective of the first study was to determine mediator release after systemic and large local reactions to subcutaneous AIT. Participants provided urine and blood samples within 30 to 90 minutes of either an SR or an large local reaction (LLR) and 4 to 6 weeks later when they were not experiencing a reaction. SRs were defined as any symptom or sign beyond the local site of injection that was deemed associated with the injection by the participant's provider. An LLR was defined as a wheal greater than 25 mm in diameter at the site of injection. The objective of the second study was to explore baseline predictors of future SRs. The second study comprised participants who collected urine and blood samples when treatment with AIT was initiated. For both studies, individuals taking 5-lipoxygenase inhibitors or nonsteroidal anti-inflammatory drugs were excluded. Both studies were approved by the Institutional Review Board.

The urine samples were tested for N-methylhistamine (NMH) and 11-BPG. The NMH (liquid chromatography-tandem mass spectrometry; normal range, 30–200 μ g/g creatinine) and 11-BPG

(enzyme immunoassay; normal range, <1,000 ng/24 hour collection and reported in this study normalized to milligrams creatinine⁵) tests have been validated and are available through our institution's clinical laboratory for a 24-hour collection sample. We also collected spot urine samples in the second study as we anticipated this collection method to be more feasible for clinical use. The serum samples were tested for tryptase (normal range, <11.5 ng/mL) by our institution's clinical laboratory. Mediator values were compared using the signed rank test (2 samples) and the Kruskal-Wallis test (3 samples).

Eight participants were enrolled (5 with SR and 3 with LLR) in the first study. The mean age was 36 years old, and 63% were female. Serum tryptase and 24-hour urine collections for NMH were within normal limits for all participants except for 1 SR participant, who had an elevated serum tryptase level in both reaction (13.1 ng/mL) and nonreaction samples (12.2 ng/mL). Twenty-four-hour urinary excretion of 11-BPG in patients with SR were elevated in 3 of 5 patients (918, 1,378, 1,069 pg/mg creatinine) in the reaction sample and 1 of 5 of nonreaction samples (1,404 pg/mg creatinine) ($p > 0.05$).

Ten patients (none of whom participated in the first study) were enrolled in the second study, 2 of whom experienced an SR and 4 an LLR over the course of their treatment period ranging from 9 to 18 months. The mean age was 32 years old; 70% were female, and none were receiving venom immunotherapy. Baseline 24-hour collections of 11-BPG and NMH strongly correlated with spot collections ($r^2 = 0.76$ and 0.89 , respectively). Tryptase levels in the 2 patients experiencing an SR were not elevated (2.3 and 4.1 ng/mL) in baseline samples, nor were 11-BPG (353 and 312 pg/mg creatinine) or NMH (64 and 122 μ g/g creatinine). If we compared all

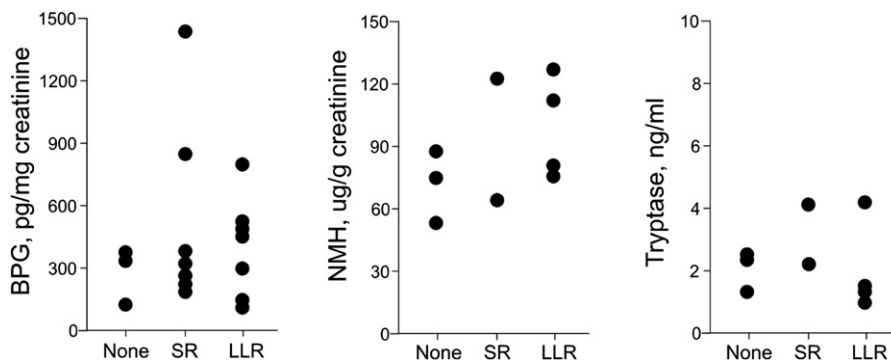


Figure 1. Baseline levels of mediators for participants who had systemic reactions, large local reactions, and no reactions. BPG, 11- β -prostaglandin; F₂- α ; NMH, N-methylhistamine (both urine samples); tryptase (serum sample); SR, systemic reaction; LLR, large local reaction.

patients in both studies in terms of baseline tryptase, 11-BPG, and NMH between those experiencing an SR, LLR, or no reaction, no significant differences were seen between groups (Fig. 1; $P > 0.05$ for 3-way comparison).

Our results suggest that 11-BPG may be elevated during SRs to AIT. Because of smaller than expected enrollment for the second study, we were unable to determine whether baseline 11-BPG levels predict SR to AIT, or to confirm that baseline tryptase predicts SRs in a nonvenom IT sample. Similar to a previous venom IT study in children of a similar sample size,⁴ we were unable to demonstrate that baseline 11-BPG levels predict SRs. Developing a prediction model that includes baseline 11-BPG would require a larger sample size, as was demonstrated for baseline serum tryptase by Reuff et al.³

An elevation in 11-BPG during SRs to AIT suggests the possibility of another approach to prevent future SRs in such patients: using aspirin preventatively before receiving an AIT injection. A previous report suggests that targeting PGD₂ with aspirin in patients with mastocytosis can significantly reduce symptoms.⁶ Given that PGD₂ release after anaphylaxis onset remains elevated for approximately 6 hours,⁵ a focused collection period after SR may help predict which patients may benefit by targeting PGD₂.

In conclusion, a PGD₂ metabolite (11-BPG) may be elevated in SRs to AIT; however, we were unable to determine whether 11-BPG is an independent predictor of risk for SR to AIT.

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