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Immune Pharmacodynamic Responses of the Novel Cancer Immunotherapeutic Imprime PGG in Healthy Volunteers

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KEY POINTS:

- The pharmacological activity of Imprime is dependent on naturally occurring serum ABA.
- A threshold of IgG ABA is necessary for Imprime-mediated innate immune responses.
- It is likely that high-ABA subjects will be more prone to infusion-related reactions.

Abstract

Imprime PGG (Imprime) is an i.v. administered, yeast β-1,3/1,6 glucan in clinical development with checkpoint inhibitors. Imprime-mediated innate immune activation requires immune complex formation with naturally occurring IgG anti-β glucan Abs (ABA). We administered Imprime to healthy human volunteers to assess the necessity of ABA for Imprime-mediated immunopharmacodynamic (IPD) changes. Imprime (4 mg/kg) was administered i.v. in single and multiple infusions. Subsets of subjects were premedicated with antihistamine and corticosteroid. Peripheral blood was measured before, during and after Imprime administration for IPD changes (e.g., ABA, circulating immune complexes, complement activation, complete blood counts, cytokine/chemokine, and gene expression changes). IPD changes were analyzed based on pretreatment serum ABA levels: low-ABA (<20 μg/ml), mid-ABA (≥20–50 μg/ml), and high-ABA (≥50 μg/ml). At the end of infusion, free serum ABA levels decreased, circulating immune complex levels increased, and complement activation was observed. At ∼1–4 h after end of infusion, increased expression of cytokines/chemokines, a 1.5-4-fold increase in neutrophil and monocyte counts and a broad activation of innate immune genes were observed. Low-ABA subjects typically showed minimal IPD changes except when ABA levels rose above 20 μg/ml after repeated Imprime dosing. Mild-to-moderate infusion-related reactions occurred in subjects with ABA ≥20 μg/ml. Premedications alleviated some of the infusion-related reactions, but also inhibited cytokine responses. In conclusion, ABA levels, being critical for Imprime-mediated immune activation may provide a plausible, mechanism-based biomarker to identify patients most likely to respond to Imprime-based anticancer immunotherapy.