Imprime PGG Drives Innate Immune Activating Pharmacodynamic Changes in a Phase I Clinical Study in Healthy Human Volunteers

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Abstract

Imprime PGG (Imprime) is currently in clinical development as combination therapy with chemotherapy. Imprime, a glycosylated, soluble β-1,2-L-fucan, is a Pathogen Associated Molecular Pattern (PAMP) that complements endogenous beta glucan antibodies (ABA) and activates innate immune effector cells to trigger the anti-cancer immune cycle. In this study, we sought to investigate the immunopharmacodynamic (IPD) response of Imprime in healthy human subjects.

Methods

Cohort 1 (n=12) received a single IV infusion of Imprime 4 mg/kg. Cohort 2 (n=12) received three weekly infusions of 4 mg/kg Imprime. Cohort 1 (n=12) received infusions of 6 mg/kg or 2 mg/kg Imprime on weeks 1, 2 and 5. In cohorts 1 and 2, six subjects each were monitored and 6 were followed. Subjects were monitored at 1, 2, 4 and 8 hours and for 24 hours post-infusion, then weekly for 4 weeks. Subjects were administered 2 mg/kg Imprime weekly for 4 weeks. Subjects were monitored at various times before, during and after Imprime administration.

Results

Acute responses of complement activation products, CD40 and ICAM-1 were detected at the end of infusion. 6 mg/kg increase in neutrophil and monocyte numbers were seen 4 hours post-infusion. Disappearance, especially in CD8 and CD16/16, were consistently detected at 24 hours. Cellular analyses showed Imprime binding to neutrophils, monocytes, subsets of DC and 7 cells. In other subjects, population of intermediate monocytes expressing higher levels of the activation markers CD69, CD14 and HLA-DR, and activation profiles after week post-infusion, increased washed monocytes and platelets were detected. Consistent increase in expression of innate immune cytokine and chemokine levels was evident in 6 mg/kg. ABA and cytokine changes were log 2 transformed. Data presented are from subjects who were treated with Imprime without multiple doses. All assays performed as described in figure legends 1 and 2.

Conclusions

• Imprime-induced IPD changes are ABA dependent
  - >20 µg/ml no response
• Pre-medications (corticosteroids and anti-histamine) dampen Imprime-mediated cytokine induction.
• Imprime-driven IPD responses are dose-dependent. Doses 2 and 4 mg/kg Imprime IPD responses were similar in subjects with ABA > 50 µg/ml.

Acknowledgements

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APA and AE (Single Dose)

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ABA and AE (Multiple Dose)

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A. Gene expression

B. Circulating immune complexes

C. Complement activity

D. Cytokines/monocytosis profile

Imprime Induces IPD Changes with Increasing ABA levels - Multiple doses

- ABA levels and indicated by red (<20 µg/mL), black (20-50 µg/mL) or blue lines (>50 µg/mL). Filled lines shown. All assays performed as described in figure legends 1 and 2.

Imprime-driven IPD responses are dose-dependent. Doses 2 and 4 mg/kg Imprime IPD responses were similar in subjects with ABA > 50 µg/ml. Subjects with mid ABA levels (20-50) showed minimal Imprime-mediated cytokine induction.

Figure 1. Imprime drives innate immune activating pharmacodynamic changes in healthy volunteers.