Characterization of metabolic response to AG-348, an allostERIC activator of red cell pyruvate kinase, in healthy volunteers and pyruvate kinase deficiency patients


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BACKGROUND
PK deficiency
• Pyruvate kinase (PK) deficiency is a glycolytic enzymopathy that causes lifelong chronic hemolytic anemia.
• PK deficiency is caused by abnormalities of the PK red blood cell isoform (PK-R) due to mutations in the PKLR gene.
• Mutations in PK-R typically affect protein stability, catalytic activity, or both, which adversely affects glycolysis and leads to reduced energy availability in red blood cells.

RESULTS
• Phase 1 studies of AG-348 in healthy volunteers (NCT02108106, NCT02149966) have been completed, and a phase 2 study in patients with PK deficiency is ongoing (NCT02481815).

METHODS
• Metabolic profiling and stable isotope tracing experiments were conducted in blood from healthy volunteers (n=10) and PK deficiency patients (n=5) receiving AG-348.

CONCLUSIONS
• A >50% increase in glycolytic flux was observed in PK deficiency patients treated with AG-348 who had a hemoglobin increase >1.0 g/dL, but was not observed in patients without such an increase.
• Metabolic markers of immature red cells are reduced in PK deficiency patients that respond to AG-348.
• Strong homeostatic regulation of overall rates of glycolysis was observed in healthy volunteers, even in the presence of activated PK-R.
• These data demonstrate that hemoglobin increases in PK deficiency patients treated with AG-348 are associated with increased red cell glycolysis.

Disclosures
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