Genotype-response correlation in DRIVE PK, a phase 2 study of AG-348 in patients with pyruvate kinase deficiency

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INTRODUCTION

Pyruvate kinase (PK) deficiency is a congenital hemolytic anemia caused by mutations in the PKLR gene, leading to a deficiency of this glycolytic enzyme and low PK-R protein levels. AG-348 is an allosteric activator of PK-R that activates the wild-type (WT) and range of rsyn PK-R enzymes associated with PK deficiency (Figure 2). Increased PK-R activity and ATP levels in patient red blood cells treated with AG-348 (2 µM) may be linked to PKLR genotype and PK-R protein levels (Figure 3). In a phase 2 clinical study of patients with PK deficiency (DRIVE PK; NCT02747016), 26 of 52 patients (50%) experienced a maximum Hb increase of >1.0 g/dL (mean maximum increase, 3.4 g/dL, range, 1.1–5.8 g/dL), including 25 of 52 patients (59.5%) with at least one missense mutation (Figure 4).

METHODS

Whole blood samples were collected from patients with PK deficiency enrolled in the phase 2 DRIVE PK study. Patient genotypes were determined by Centogene AG (http://www.centogene.com). Levels of PK-R protein were quantitated using a Menz Scope assay as described previously (antibodies from Alomone, Cambridgeshire, UK [ab79057] and Aviva Systems Biology, London, UK [OAGA00912]). The signal was normalized to a reference control sample from a subject without PK deficiency.

RESULTS

An association between baseline PK-R protein level and maximum Hb change was observed in DRIVE PK patients (Figure 5). An association was also observed between baseline PK-R protein levels and the number of missense mutations (Figure 6). A statistically significant correlation was observed between Hb increases and patient genotype, biochemical response to AG-348 treatment, and baseline PK-R protein level (Figure 7). A statistically significant correlation was observed between PK-R activity and ATP levels in red blood cells treated with AG-348 (2 µM) vs no AG-348 (2 µM) in the presence of increasing concentrations of PEP (Figure 8). Figure 9 illustrates the relationship between Hb increase and patient genotype, biochemistry, response to AG-348 treatment, and baseline PK-R protein level.

SUMMARY AND CONCLUSIONS

• This study demonstrates that patients with at least one B3001 or R479H missense mutation have lower PK-R protein levels than patients with other missense mutations (Figure 10).

• This correlation is evidence that AG-348 is working via its proposed mechanism of action of stimulating the residual activity of the mutant enzyme.

• Although neither genotype-nor PK-R protein level could predict Hb increases with absolute precision, some trends were observed: Patients with two non-missense mutations had lower protein levels than those with at least one missense mutation. Patients with R479H or R830Q mutations had lower protein levels than patients with other missense mutations.

• These preliminary findings will be examined further in the ongoing phase 3 studies of AG-348 (NCT03562220 and NCT03559999).

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Disclosures

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