Correlation of Voxelotor Exposure With Hemoglobin Response and Measures of Hemolysis in Patients From the HOPE Study

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BACKGROUND

• Sickle cell disease (SCD) is an inherited disorder in which pathology is driven by hemoglobin (Hb) polymerization and red blood cell sickling, leading to chronic hemolysis and anemia as well as episodic vaso-occlusion.1
• Hemolytic anemia has been consistently associated with vasculopathic complications, including stroke and pulmonary hypertension.2
• These manifestations of SCD contribute to cumulative organ damage, which leads to disability and accelerated mortality.3

• Voxelotor is a first-in-class soluble Hb polymerization inhibitor being developed for the treatment of SCD. In the phase 3 HOPE trial, voxelotor 1500 mg and 800 mg administered orally once daily demonstrated sustained and dose-dependent improvements in Hb levels and reductions in measures of hemolysis compared with placebo.3

OBJECTIVE

To evaluate the association between Hb response and measures of hemolysis in voxelotor-treated patients in the phase 3 HOPE trial in a post hoc analysis.

METHODS

Study Design

A post hoc analysis of the data from the HOPE trial was performed. The HOPE trial was a phase 3, randomized, placebo-controlled, double-blind, multicenter study comparing the efficacy and safety of 2 different doses of voxelotor with placebo in patients with SCD who were aged 12 to 65 years (Figure 1).3

• The primary endpoint was the percentage of patients with a Hb response at week 24, defined as a ≥1.5 g/dL increase in Hb from baseline.

• Secondary endpoints included changes in markers associated with hemolytic: absolute reticulocyte count, percentage of reticulocytes, indirect bilirubin level, and lactate dehydrogenase (LDH) level.

RESULTS

Baseline Characteristics

The baseline characteristics were similar across treatment and placebo groups, as presented in Table S1.

Measures of Hemolysis Were Lower in Voxelotor-Treated Patients

Among patients receiving voxelotor, all measures of hemolysis were consistently lower for those with increases in Hb of ≥1.5 g/dL than for those with changes of <1.5 g/dL (Figure 2). Changes in Hb were consistent with voxelotor treatment compared with placebo, but no differences were noted in reticulocytes, LDH, or lactate dehydrogenase (LDH) level. Figure S2 shows that changes in Hb were consistent with voxelotor treatment compared with placebo.

CONCLUSIONS

• Treatment with voxelotor was associated with reductions in indirect bilirubin level, LDH level, absolute reticulocyte count, and percentage of reticulocytes.

• Among patients treated with voxelotor, those with Hb increases of ≥1.5 g/dL had the greatest reduction in these markers; those with Hb increases of ≥1.5 g/dL experienced a greater reduction in reticulocyte levels than patients who did not have an increase in Hb.

• Decreases in measures of hemolysis correlated with increases in voxelotor whole blood concentrations.

• These results suggest that the mechanism by which voxelotor raises Hb is related to a reduction in hemolysis, which may modify the morbidity of SCD by improving hemolytic anemia.

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REFERENCES


DISCLOSURES

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