Targeted Agent Offers Treatment for Sickle Cell Disease

Voxelotor, a sickle hemoglobin (HbS) polymerization inhibitor, shows promise in treating patients with sickle cell disease.

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August 12, 2019 – Oral administration of voxelotor increased hemoglobin levels and reduced hemolysis in patients with sickle cell disease, a new phase 3 study reports.

Elliott Vichinsky, MD, and colleagues at the University of California, San Francisco Benioff Children's Hospital Oakland, in Oakland, California, reported their findings in the August 8, 2019 issue of *The New England Journal of Medicine*.

In patients with sickle cell disease, the polymerization of deoxygenated HbS underlies the pathogenesis of the disease. Voxelotor reversibly binds to hemoglobin and stabilizes the molecule in the oxygenated state. Increasing the proportion of oxygenated HbS inhibits HbS polymerization, which, it is hypothesized, should reduce disease severity.

Previous studies showed that oral administration of voxelotor decreased red-cell sickling, reduced blood viscosity, and improved red-cell deformability in vitro; it also increased the half-life of red cells, and reduced anemia and hemolysis in vivo.

In the current study, 274 adolescents and adults aged 12 to 65 with sickle cell disease were randomly assigned in a 1:1:1 ratio to receive an oral dose of 1500 mg voxelotor, 900 mg voxelotor, or placebo.

The primary endpoint of the study was the percentage of participants demonstrating a hemoglobin response, defined as an increase in hemoglobin level from baseline of greater than 1.0 g per deciliter at week 24. The researchers state that they used this measure "because validated natural history studies indicated that an increase in hemoglobin level significantly decreases the rate of multiorgan failure and death." A significantly higher proportion of patients receiving 1500 mg voxelotor showed a hemoglobin response (51%; 95% CI, 41 to 61) compared with those receiving placebo (7%; 95% CI, 1 to 12) ($P<0.001$).

Secondary endpoints included the annualized incidence rate of vaso-occlusive crisis, as well as laboratory markers associated with hemolysis, including the indirect bilirubin level and percentage of reticulocytes. The decrease in indirect bilirubin from baseline to week 24 was significantly greater among patients receiving 1500 mg voxelotor compared with those receiving placebo (mean change, −29.1% vs. −3.2%; $P<0.001$). The relative change in the percentage of reticulocytes was significantly greater for patients receiving 1500 mg voxelotor (a mean decrease of −19.9%) compared with placebo (a mean increase of 4.5%; $P<0.001$). Among the three treatment groups, the incidence of vaso-occlusive crisis did not differ significantly.

Headache and diarrhea were the most common adverse events; the incidence was 20% or greater for each. Most adverse events were grade 1 or 2. The proportion of patients who had an adverse event of at least grade 3, a serious adverse event, or discontinuation of therapy based on an adverse event was not substantially different among the treatment groups.

Overall, "voxelotor provided a significant, sustained increase in hemoglobin level and reduced the incidence of worsening anemia and hemolysis in persons with sickle cell disease," the investigators conclude. "Long-term follow-up studies are planned to evaluate the effect of the increase in hemoglobin level and decrease in hemolysis induced by voxelotor on morbidity and mortality," they add.

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