Novel small molecule therapy shows benefit for anemic patients via hydration of red blood cells

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Researchers are identifying innovative therapeutics for sickle cell anemia that focus on specific factors in the disease's progression, such as the important role of hydration of the red blood cells. According to a study prepublished online in *Blood*, the official journal of the American Society of Hematology, a novel small molecule therapy called senicapoc showed efficacy in maintaining hydration of red blood cells and increasing hemoglobin levels in patients with sickle cell anemia. Sickle cell anemia affects about 70,000 Americans, and millions worldwide.

Sickle cell anemia (the most common form of sickle cell disease, or SCD) is a serious chronic condition in which the red blood cells (RBCs) can become sickle-shaped upon deoxygenation (shaped like a "C"). Because of their shape, rigidity, and tendency to stick to blood vessel walls, the cells do not move easily through the vessels and can form clumps, which may lead to blocked blood flow and pain, infections, or organ damage.

Research suggests that dehydration of the RBCs is one of the key contributors to the deformed shape and affects the levels of circulating hemoglobin, an important determinant of oxygen delivery throughout the body. The dehydration appears to result from loss of potassium via two pathways, one of which is known as the Gardos channel. It has been suggested that a therapy designed to block this channel might have a beneficial effect on the progression of the disease.

Senicapoc, a known Gardos channel blocker, works by limiting solute and water loss, thereby preserving RBC hydration. Previous studies have shown that senicapoc prevents the loss of potassium from the RBCs, is well tolerated, and has favorable pharmacokinetics with a long half-life, permitting once-daily dosing.

In a 12-week, multicenter, phase II, randomized, double-blind, dose-finding study, senicapoc was evaluated for its effect on hemoglobin level and markers of RBC destruction (hemolysis) in SCD patients. The investigators also sought to obtain additional safety data and identify the optimal dose for a phase III study. The primary efficacy endpoint was the change in blood hemoglobin level from baseline to end of study, and secondary endpoints included markers of hemolysis, changes in RBC count and indices, and frequency of painful events or "crises."

"An understanding of the pathophysiology of sickle cell disease is extremely important in order to identify new therapeutic targets," said Kenneth Ataga, MD, of the Division of Hematology/ Oncology at the University of North Carolina at Chapel Hill and lead author of the study.

A total of 90 eligible patients were enrolled in the trial. Of these participants, 24 were also taking hydroxyurea, a drug already approved for the treatment of SCD. The patients were randomized into three treatment arms: placebo (n=30), low-dose senicapoc (6 mg/day, n=29), and high-dose senicapoc (10 mg/day, n=31). Safety and efficacy assessments were obtained at the end of week one and then every two weeks until completion of the study treatment.

Patients treated with senicapoc achieved measurable improvements in hemoglobin levels. Patients in the high-dose senicapoc arm achieved a hemoglobin increase of 0.68 g/dL (vs. 0.01 g/dL for patients taking placebo). The team also found corresponding increases in hematocrit and RBC count in the patients taking senicapoc when compared to placebo.

Notably, the sub-groups of patients taking hydroxyurea achieved similar results. In the low-dose group, the increase in hemoglobin compared to placebo was not statistically significant.

Treatment with senicapoc also produced dose-dependent and statistically significant improvements in secondary endpoints, including the percentage of dense RBCs (-2.41 vs. -0.08, high-dose vs. placebo), reticulocytes (-4.12 vs. -0.46), and lactate dehydrogenase (-121 vs. -15), a marker of hemolysis. There were no differences among the treatment groups in the overall frequency of painful crises, though crises experiences were infrequent in this study.

Senicapoc was safe and well tolerated in the study. Ten patients, five of whom were in the placebo group, discontinued the study early. Three patients dropped out due to adverse events: one in the low-dose group for weakness and shortness of breath, and two in the high-dose group for pain crises and acute chest syndrome. The most common serious adverse effect (SAE) was pain crisis, followed by pneumonia and acute chest syndrome, with a similar incidence across the active and placebo arms. None of the SAEs were thought attributable to senicapoc.

"The results we saw in this study provide further evidence that blocking the Gardos channel reduces dehydration of the sickle erythrocytes and thus supports the hypothesis that this type of approach may lead to an amelioration of the anemic state in patients with sickle cell anemia," said Dr. Ataga. "As noted in the paper, a Phase III study of senicapoc in SCD patients was recently terminated due to the low probability of achieving a reduction in crisis rate, the primary endpoint of that study. Clearly, further work is necessary to understand how the reduction in RBC dehydration and hemolysis demonstrated from the results of this Phase II study impacts the complex pathophysiology of sickle cell disease."

Source: American Society of Hematology