Thalidomide analog appears worthy opponent of sickle cell disease

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A thalidomide analog is shaping up as a safe, worthy opponent of sickle cell disease, Georgia Health Sciences University researchers report.

Much like hydroxyurea, the only Food and Drug Administration-approved therapy for sickle cell, pomalidomide increases production of fetal hemoglobin which, unlike its adult counterpart, cannot take on the destructive sickle shape.

In stark contrast, pomalidomide also preserves bone marrow function actually increasing proliferation of the cells that make oxygen-carrying red blood cells, GHSU researchers report in the journal *Blood*. Hydroxyurea is known to suppress bone marrow function, potentially leaving patients susceptible to infection and bleeding.

"We were thrilled to find that pomalidomide stimulated fetal hemoglobin expression without toxicity to the bone marrow and increased productions of red blood cells in the face of anemia," said Dr. Steffen E. Meiler, anesthesiologist, Vice Chairman of Research in the GHSU Department of Anesthesiology and Perioperative Medicine and the study's corresponding author.

The study compared pomalidomide to hydroxyurea as well as a combination of the drugs in a mouse model of sickle cell disease. After eight weeks, both pomalidomide and hydroxyurea increased fetal hemoglobin but only pomalidomide was kind to the bone marrow. Surprisingly, when the drugs were given together, all benefits were lost.

"We are excited and optimistic about pomalidomide doing the same thing for patients meaning it will boost their fetal hemoglobin and boost their red blood cells," said Dr. Abdullah Kutlar, Director of the GHSU Sickle Cell Center and a study co-author. "If we can do that, it will be the best of both worlds," added Kutlar also is a principal investigator on a phase 1 trial pursuing the drug's patient potential.

Despite its notorious reputation for causing birth defects, thalidomide and now its analogs are carving out a potentially positive future for their ability to regulate the immune response. In fact, it was the inflammation-fighting ability of the analog lenalidomide that GHSU researchers wanted to study. Inflammation, another sickle cell disease hallmark, results when white blood cells attack the abnormal- looking red blood cells as well as the sickle-shaped cells injuring the blood vessel wall lining.

Lenalidomide already is approved for anemia as well as a cancer of the white blood cells called multiple myeloma and is currently under study for other cancers. When GHSU researchers approached drug-maker Celgene Corporation about the study, the New Jersey-based company shared laboratory evidence that pomalidomide, a more potent and closely related cousin of lenalidomide, had the added benefit of increasing fetal hemoglobin expression and proliferation of CD34+ progenitor cells, which make red blood cells. When the researchers looked at pomalidomide's impact on fetal hemoglobin and bone marrow function in their mouse model, they found similar results.

"Pomalidomide produced about as much fetal hemoglobin as hydroxyurea but the bone marrow was entirely intact," Meiler said. The laboratory work prompted them to initiate a Phase 1 clinical trial of the drug for sickle cell disease with Wayne State University in Michigan. Because of past experience with thalidomide, women of child-bearing age receive a pregnancy test and contraception counseling before

entering the study. Participants taking pomalidomide also can't have taken hydroxyurea for at least several months to help ensure any results are from the newer drug.

Sickle cell is a genetic disease affecting 1 in 500 blacks in the United States.

Provided by Georgia Health Sciences University