Researchers team on sickle cell clinical trial

July 20 2010

Researchers from the La Jolla Institute for Allergy & Immunology have joined forces with the Dana-Farber Cancer Institute in Boston and Washington University in St. Louis to investigate a potential new therapy for sickle cell disease, a severe and chronic illness affecting more than 70,000 Americans and several million people worldwide. A drug called Lexiscan (regadenoson - Astellas Pharma US,Inc.), approved by the Food and Drug Administration as a pharmacologic stress agent used to diagnose heart disease in some patients, will be tested in the multi-center clinical trial. Patient recruitment for the trial is under way.

"We will be testing the ability of Lexiscan to reduce inflammation that contributes to the poor blood flow and serious complications characteristic of sickle cell disease," said the La Jolla Institute's Joel Linden, Ph.D., a prominent scientist whose research laid the groundwork for the trial. "We are hopeful that this therapy will prove important in improving and extending the lives of sickle cell patients."

The trial, to be conducted at sites in Boston and St. Louis, is being funded primarily by a $1.2 million, 2-year American Recovery and Reinvestment Act (ARRA) stimulus grant from the National Heart Lung and Blood Institute, part of the National Institutes of Health. Dr. Linden and David G. Nathan, M.D., president emeritus of the Dana-Farber Cancer Institute, former physician-in-chief at Children's Hospital Boston, and one of the world's top sickle-cell experts, are co-investigators leading the project.

Dr. Linden and his team at the La Jolla Institute will analyze blood

samples from participants, which will be collected from adults at two trial sites: Brigham and Women's Hospital in Boston, and Washington University in St. Louis, Missouri. Pending these results, a trial site for children 14 years of age and older is planned at Children's Hospital Boston in the study's second year.

Dr. Nathan, who will direct the clinical component of the trial, said he is excited by the prospect of reducing some of the worst symptoms of sickle cell disease, particularly pain and severe breathing problems, known as acute chest syndrome. Patients with the severest form of the disease typically do not live beyond their mid-40s or 50s, with pulmonary problems being the most common cause of death.

Lexiscan is a pharmacologic stress agent indicated for radionuclide myocardial perfusion imaging (MPI), a type of imaging test used to analyze arterial blood flow to help in the diagnosis of heart disease. Lexiscan is used in patients unable to undergo adequate exercise stress testing. It is given in brief (10 seconds), intravenous doses during coronary stress testing. The new trial will test smaller doses of Lexiscan, administered for longer periods of time to potentially suppress inflammation.

Dr. Linden has been researching the effects of adenosine, a signaling molecule similar to the active ingredient in Lexiscan, in mouse models of sickle cell disease for the last four years. A world-renowned expert on adenosine, Dr. Linden said adenosine binds to receptors known to be important in blocking inflammation. In his studies, Dr. Linden found that adenosine significantly reduced inflammation and pulmonary defects in the sickle cell mice.

In sickle cell disease, also known as sickle cell anemia, the body's oxygen-carrying red blood cells become stiff, sticky and misshapen or "sickled" in appearance and clog the body's small blood vessels. This

leads to reduced blood flow and lower oxygen levels, causing symptoms such as anemia, pain crises, organ damage or even death. Inflammation caused by white blood cells of the immune system has been shown to significantly exacerbate sickle cell disease.

An inherited disorder, sickle cell disease primarily affects those of African descent and Hispanics of Caribbean ancestry, but the trait has also been found in those with Middle Eastern, Asian, Indian, Latin American, Native American, and Mediterranean heritage.

In the U.S., it is estimated that more than 70,000 people, primarily African-Americans, are affected by the disease. Sickle cell disease occurs in individuals who inherit two copies of the sickle cell gene—one from each parent. Millions worldwide are estimated to suffer complications from sickle cell disease.

The trial will begin in adults with sickle cell disease but no painful crises, giving different test doses of Lexiscan for periods of 12 and 24 hours to ensure that it does not cause toxicity. Pending these results, the team will then move to test Lexiscan in adults with pain crises and acute chest syndrome, and, in the second year, in children age 14 and older.

Dr. Nathan, who for three decades led the Division of Hematology at Children's Hospital Boston and later the joint Hematology and Oncology program of Children's and Dana-Farber Cancer Institute, hopes Lexiscan will reduce the severity of life-threatening acute chest syndrome. "Pulmonary complications of sickle cell anemia can be fatal, because patients are unable to breathe," he said. "We want to see if the drug will abort pulmonary injury. We do know that it works very well in sickle cell mice with pulmonary disease," he said referring to Dr. Linden's ongoing adenosine research.

In his studies, Dr. Linden not only showed that adenosine significantly

reduced inflammation and pulmonary defects in mouse models of sickle cell disease, he also pinpointed the specific white blood cells causing the inflammation, known as invariant natural killer T cells or iNKT cells.

Dr. Linden, working in conjunction with Joshua Field, M.D., a hematologist from Washington University, found that patients with sickle-cell disease have significantly elevated numbers of activated iNKT cells. "This further validated that inflammation plays a major role in this disease," he said.

Provided by La Jolla Institute for Allergy and Immunology