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New sickle cell anemia therapy advances to Phase II clinical trials

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Seeking to improve the lives of sickle cell anemia sufferers around the world, researchers from the La Jolla Institute for Allergy and Immunology, the Dana-Farber/Children's Hospital Cancer Center in Boston and the BloodCenter of Wisconsin in Milwaukee and others are preparing to launch Phase II of a clinical trial to investigate a potential new therapy for reducing the disorder's severest symptoms. Sickle cell anemia is a serious, painful and chronic illness that impedes blood flow and can lead to early death. More than 100,000 Americans and several million people worldwide suffer from this genetic disorder.

The phase II trial, funded by a $10.8 million grant from the National Institutes of Health, is testing an already existing drug called Lexiscan (regadenoson - Astellas Pharma US, Inc.), which is used for diagnosing heart disease. Researchers are exploring whether the drug's anti-inflammatory effects will significantly reduce the pain and blood flow disturbances of sickle cell anemia. A Phase I safety study was completed earlier this year. Recruitment is now under way for the trial's second phase to be conducted at treatment centers in eight major U.S. cities: Boston, Baltimore, Detroit, Chicago, Cincinnati, Milwaukee, Chapel Hill, and St. Louis.

"We are excited to begin the next phase of investigating Lexiscan's potential for reducing inflammation that contributes to the poor blood flow and serious complications of sickle cell disease," says La Jolla Institute scientist Joel Linden, Ph.D., a prominent researcher whose studies laid the groundwork for the trial. "Our phase I results were

promising. Participants experienced no adverse reactions and our tests indicated that the drug significantly reduces inflammation. It is too early to tell whether this will translate into reduced pain and tissue damage. But we remain cautiously optimistic." The Phase I results were published as the cover article in the print edition of the journal *Blood* on April 25th, 2013.

David G. Nathan, M.D., president emeritus of the Dana-Farber Cancer Institute, who is the trial's co-lead investigator with Dr. Linden and Joshua Field, M.D., of the BloodCenter of Wisconsin, says he is excited by the prospect of reducing some of the worst symptoms of sickle cell disease, particularly periodic disease exacerbations that lead to severe pain or breathing problems, known as vaso-occlusive crises and acute chest syndrome, respectively. Patients typically do not live beyond their late 40s or early 50s, with pulmonary problems being the most common cause of death.

"Pulmonary complications of sickle cell disease can be fatal because blood flow problems restrict the amount of oxygen going to the lungs," says Dr. Nathan, former physician-in-chief at Boston Children's Hospital and one of the world's top sickle-cell experts. "We are hopeful that the drug will reduce pulmonary injury and extend the lives of sickle cell patients."

In sickle cell anemia, the oxygen-carrying red blood cells become stiff, sticky and misshapen or "sickled" in appearance. This leads to poor blood flow that deprives tissues of oxygen and causes symptoms such as severe pain, difficulty breathing and damage to multiple organs. An inherited disorder, sickle cell anemia occurs in individuals who inherit two copies of the sickle cell gene—one from each parent. It is most common in persons of African descent, but is also found in Hispanics of Caribbean ancestry, and people of Middle Eastern, Asian, Indian, Latin American, Native American, and Mediterranean heritage.

"I treat patients with sickle cell anemia in my clinic every day," says Dr. Field. "It is a devastating disease and therapies for the two most common complications, pain and acute chest syndrome, are very limited. Lexiscan has the potential to help people with sickle cell anemia by decreasing the severity of these life-threatening problems."

The sickle cell trial grew out of research by Dr. Linden, who is a leading expert on adenosine receptors, which are known to act as a natural brake on inflammation. While Dr. Linden had previously explored adenosine's role in protecting tissues from damage due to low blood flow in single tissues such as in heart disease, he was struck one day with the idea that it might also protect people with sickle cell disease, who suffer tissue damage from poor blood flow to most tissues.

Dr. Linden began testing his theory in mouse models about four years ago and found that adenosine-like compounds significantly reduced the damaging effects of the disease. He was aware of an existing FDA approved adenosine-like drug, Lexiscan™ that had already been approved for another use. "This was good news since it meant that Lexiscan was known to be safe in humans and could probably gain rapid approval if proven effective in clinical trials as a treatment for sickle cell disease," he said.

Dr. Linden joined forces with Dr. Nathan, who participated in the development of the only existing FDA-approved drug for sickle cell treatment, hydroxyurea, and another clinical collaborator, Dr. Field, to seek NIH funding for the Lexiscan trial. They launched the trial's first phase in 2010 using patient volunteers from Brigham and Women's Hospital in Boston and Washington University in St. Louis.

In the trial, Dr. Nathan, Dr. Field and other clinicians collected blood from patients and sent it to Dr. Linden in La Jolla for analysis of white blood cell inflammation. Gene Lin, Ph.D., a scientist in Linden's lab, has

been a significant contributor to the analysis effort. The same protocol will be used in the trial's second phase.

Lexiscan is approved as a pharmacologic stress agent used for myocardial perfusion imaging (MPI), a procedure that measures coronary blood flow to help in the diagnosis of heart disease. Lexiscan is used in patients too ill to undergo exercise stress testing using a treadmill. It is given in brief (10 seconds), intravenous doses.

In Phase I of the trial, a dose escalation safety study, participants received very low doses of Lexiscan administered by continuous intravenous infusion, over 12 or 24 hours, to suppress inflammation. Following this initial study of adults with sickle cell anemia not experiencing pain crises, Phase II of the trial will expand to include patients experiencing pain crises and acute chest syndrome, and children over 14. Dr. Linden adds that Phase II will be a placebo-controlled trial.

Provided by La Jolla Institute for Allergy and Immunology