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Anti-platelet therapy does not significantly reduce pain crises in sickle cell disease

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Treatment with the antiplatelet agent prasugrel does not significantly reduce the rate of pain crises or severe lung complications in children with sickle cell disease, according to a report published in the *New England Journal of Medicine* describing one of the largest and most geographically diverse international clinical trials on sickle cell disease to date.

The Determining Effects of Platelet Inhibition of Vaso-Occlusive Events (DOVE) trial (ClinicalTrials.gov NCT01794000) was a double blind, randomized, placebo-controlled phase 3 clinical trial held at 51 sites across 13 nations in the Americas, Europe, the Middle East, Asia and Africa. Led by researchers at Dana-Farber/Boston Children's Cancer and Blood Disorders Center and UCSF Benioff Children's Hospital Oakland, the goal of the trial was to determine whether prasugrel, a medication used in adult patients to reduce thrombotic cardiovascular events, could also significantly reduce the rate of rate of vaso-occlusive crises (VOCs)—defined as pain crises or acute chest syndrome—in children with sickle cell disease.

Sickle cell disease affects approximately 100 million children and adults globally, largely in sub-Saharan Africa, the Middle East and India. In the United States, where it affects only about 100,000 children and adults, primarily of African-American descent, it is classified as an orphan disease. Patients with this inherited blood disorder often experience repeated pain crises related to interrupted blood flow in small vessels triggered by the complicated interactions among stiff, sticky, sickle-

shaped red blood cells; infection-fighting white blood cells; clot-producing platelets; and the endothelial cells lining blood vessel walls. These crises starve downstream tissues of oxygen and trigger pain and inflammation. Over time, recurrent crises lead to tissue damage and chronic inflammation.

To date, the Food and Drug Administration has only approved a single drug, hydroxyurea, for the treatment of and reduction of crisis risk due to sickle cell disease. However, hydroxyurea does not work for all patients, and, although it is often prescribed for children, it is only approved for use in adult patients.

"Sickle cell disease has a very complex, multisystem pathophysiology," said Matthew M. Heeney, MD, clinical director of the Blood Disorders Center at Dana-Farber/Boston Children's and co-lead investigator of the DOVE trial. "As we learn more about this disease, we are finding that other blood cells beyond red blood cells, including platelets, have significant parts to play in the development of VOCs. There likely are additional routes by which we can intervene."

"Although we were disappointed that prasugrel does not appear to ease the suffering of children with sickle cell disease, the fact that this study incorporated patients in the wide range of countries where the disease occurs is hugely significant," added Carolyn Hoppe, MD, a pediatric hematologist/oncologist at UCSF Benioff Children's Hospital Oakland and DOVE co-lead investigator. "The logistical challenges that we addressed in designing and implementing the study can serve as a model for future research."

Prasugrel—developed and marketed by Daiichi Sankyo Company, Ltd., and Eli Lilly and Company under the brand name Effient—prevents platelets from aggregating by blocking an enzyme called P2Y12. This oral drug is approved for use in adult cardiac patients in the U.S. to

reduce the risk of clots following angioplasty or insertion of an arterial stent.

The DOVE trial enrolled 341 children with sickle cell disease, 170 of whom received daily oral prasugrel for between nine and 24 months at individualized, blinded doses intended to maintain a selected target range of platelet activity. The remaining patients received a placebo. All patients were monitored for VOCs prompting medical visits and for any increased risk of bleeding due to reduced platelet activity. In addition, patients 4 years old and older kept a daily electronic pain diary to aid in the reporting of painful events between visits.

To conduct the study successfully on such a broad geographical scale, the study team had to address several obstacles, such as varying standards of care, local technological resources and infrastructure challenges, such as a lack of reliable electrical power.

At the end of the study period, the overall rate of VOCs among patients in the trial's prasugrel arm was 2.3 episodes per person year. This rate did not differ significantly from that among placebo-treated patients (2.8 per person-year; $p = 0.12$). In addition, treatment with prasugrel did not have any significant effects on the trial's secondary outcome measures (i.e., VOC-related hospitalization rate, duration of hospitalization, time between VOCs, incidence of ischemic attack or ischemic stroke, transfusion rate, rate of pain, intensity of pain, use of analgesics or missed school due to sickle cell disease-related pain). The study investigators noted no adverse safety events related to prasugrel.

The data did reveal a trend toward reduced VOC rates among patients aged 12-18 years ($p = 0.06$) and among patients who were not taking hydroxyurea ($p = 0.06$). However, these trends also were not statistically significant and require further research to determine their validity.

"Even though prasugrel did not achieve significant results, the findings should not detract from the fact that this team successfully completed a rigorous, sophisticated trial in a disease where the barriers to conducting large-scale international, patient-focused research are quite high," said Heeney. "While we designed the study to measure the overall effect of prasugrel alone on VOCs, it may be that a different approach that incorporates anti-platelet treatment as a component could potentially have an impact."

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