Check for updates

ELSEVIER

Blood 142 (2023) 3864

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

113.SICKLE CELL DISEASE, SICKLE CELL TRAIT AND OTHER HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIAS: BASIC AND TRANSLATIONAL

Apohemoglobin-Hpatoglobin Promotes Blood Flow in Sickle Cell Disease Mice

Carlos J Munoz, MS,BS[1], Daniela Lucas, PhD[1], Cynthia R Muller, PhD[2], Srila Gopal, MD[3,4], Pedro Cabrales, PhD[5]

[1] University of California San Diego, La Jolla, CA
[2] University of California, San Diego, La Jolla, CA
[3] University of California San Diego Health, San Diego, CA
[4] Division of Hematology/Oncology, University of California San Diego, San Diego, CA
[5] Functional Cardiovascular Engineering Laboratory, University of California, San Diego, La Jolla, CA

In sickle cell disease (SCD), a single change in the β-globin gene coding sequence results in the production of hemoglobin S (HbS). This HbS polymerizes when deoxygenated, causing red blood cell (RBC) sickling, hemolysis, anemia, reduced blood flow in small vessels, activation of vascular endothelial cells, vaso-occlusion, and ischemia. These abnormalities lead to various clinical complications, including fatigue, painful vaso-occlusive crises (VOC), reduced quality of life, organ damage, and early death. The management of SCD involves supportive care, pain management, blood transfusions, and disease-modifying therapies, all aimed at alleviating symptoms and improving the overall quality of life for affected individuals.

We propose a new therapy that uses a biologic called apohemoglobin-haptoglobin (apoHb-Hp), which scavenges free circulating Hb and heme. This study examined the efficacy of apoHb-Hp in reducing vaso-occlusion in a mouse model of sickle cell disease (SCD) using transgenic mice expressing HbSS-Towne (sickle cell mice) and compared them to mice expressing normal Hb, HbAA-Towne. A single dose (10 mg/kg) of normal saline (control), Haptoglobin (Hp), or apoHb-Hp was administered before the experiment, and twenty-four subcutaneous venules were selected and mapped after baseline selection. The same vessels were re-examined for stasis at 2, 8, 24, and 48 hours, and the percentage of stasis was calculated.

The results demonstrated that microvascular stasis occurs spontaneously in the Towns transgenic mice model but can be reduced by a single dose of the apoHb-Hp complex. In another set of experiments, mice were pretreated with the apoHb-Hp complex or Hp and then challenged with hypoxia-reoxygenation (hypoxia of 10% oxygen for one hour) and followed for 48 hours. Hypoxia induced microvascular stasis, also known as vaso-occlusion, which increased post-hypoxia and slowly disappeared over time in Towns mice. The study showed that pre-treatment with the apoHb-Hp complex or Hp improved the rates of recovery from vaso-occlusive crises. A single dose of the apoHb-Hp complex also reduced vascular stasis. In the last study, we administered Hb mixed with either Ringer's lactate, apoHb-Hp complex, or Hp to Towns mice fitted with the dorsal window. We knew that exogenous Hb could cause vascular stasis in Towns mice, so we aimed to investigate the effectiveness of the apoHb-Hp complex compared to Hp in preventing Hb-induced vascular stasis. The Hb infusion led to maximal stasis within an hour in the control group. Therefore, microvascular stasis occurred one hour after infusing Hb alone or with equimolar apoHb-Hp complex and Hp. Our results showed that mice co-infused with Hb + apoHb-Hp complex or Hb + Hp had significantly lower stasis levels compared to mice infused with Hb alone. Surprisingly, the apoHb-Hp complex was more effective than Hp alone in reducing Hb-induced stasis.

These findings provide insight into the underlying mechanisms of the apoHb-Hp complex and demonstrate its efficacy in reducing vaso-occlusion. Further studies are necessary to optimize the therapeutic use of the apoHb-Hp complex.

Disclosures Gopal: *Alexion:* Speakers Bureau; *bluebird bio:* Honoraria.

https://doi.org/10.1182/blood-2023-190585

Downloaded from http://ashpublications.net/blood/article-pdf/142/Supplement 1/3864/2205246/blood-466-main.pdf by guest on 20 May 2024

© 2023 by The American Society of Hematology