Iron regulation offers new treatment hope for incurable blood cancer

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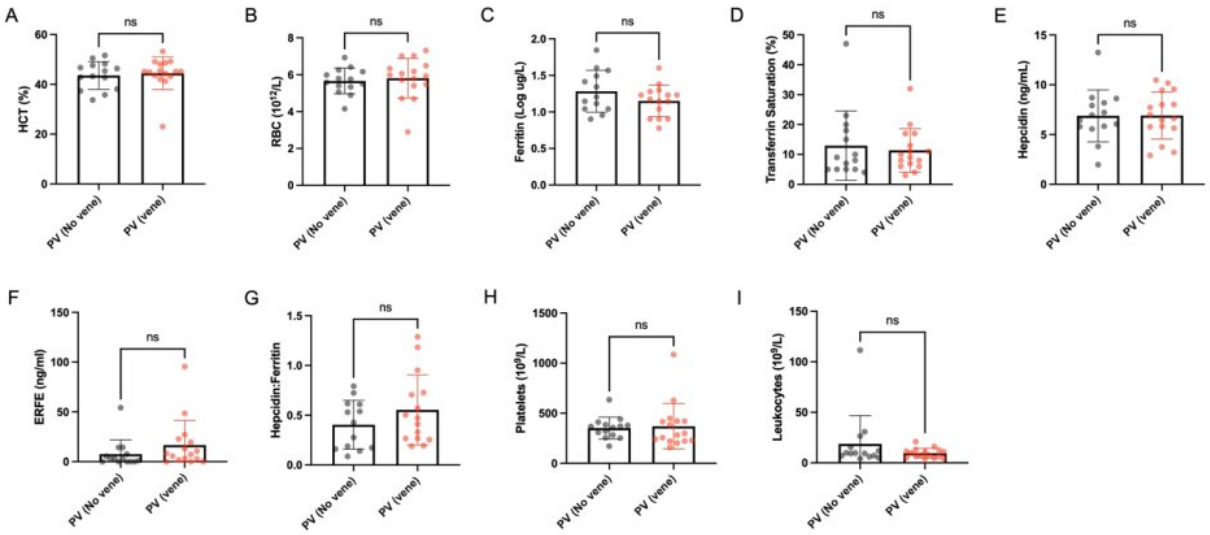

Hematological and iron markers are similar in PV patients with and without history of venesection. (A) Hematocrit (HCT); (B) red blood cell count (RBC); (C) ferritin; (D) transferrin saturation; (E) serum hepcidin; (F) serum ERFE, (G) hepcidin:ferritin ratio, (H) platelet count and (I) leukocyte count in PV patients with a history of venesection (red dots) or those without (black dots). (A, B, D-F, H-I) N=14 no vene/16 vene; (C, G) N=13 no vene/15 vene. Mann-Whitney test (A, D, F, G-I) or Unpaired 2-tailed t9 test with Welch's correction (B, C, E). ns = non-significant. Credit: *Blood* (2023). DOI: 10.1182/blood.2022016779

A landmark discovery linking iron regulation to a rare blood cancer has led to clinical trials of a potential new treatment for patients with the

incurable disease.

The study focused on polycythemia vera (PV), a blood disorder causing excessive red blood cells, and found that restricting iron access to the bone marrow could reduce the production of red blood cells in this disease.

The research, led by WEHI in collaboration with the University of Melbourne, the Peter MacCallum Cancer Centre, the University of Cambridge and Silence Therapeutics (U.K.), has led to new clinical trials of a drug that has the potential to control iron regulation in patients with PV.

An estimated 250 Australians are diagnosed with polycythemia vera (PV) each year. PV is a chronic disease and there currently is no cure.

Without treatment, PV can be life-threatening as an overproduction of red blood cells causes thicker blood, elevating a patient's risk of developing blood clots and cardiovascular conditions like heart attacks and stroke.

The cancer is currently treated with venesection, where about 500mL of blood is taken from a patient multiple times a month, to rapidly reduce their red cell count and blood thickness.

The new study, titled "Iron homeostasis governs erythroid phenotype in Polycythemia Vera," published in the journal *Blood*, provides a promising new treatment avenue that could see the often painful and disruptive blood draws replaced with a simple injection every few months.

First author, Dr. Cavan Bennett, said discovering that restricting iron access to the bone marrow could reduce the disease severity of PV was a

gamechanger.

"Through our pre-clinical studies, we found the hormone hepcidin, which is the master regulator of iron availability, is critical for controlling red blood cell production in models of this disease," Dr. Bennett said.

"The more hepcidin you have in the body, the more you restrict iron access to the bone marrow.

"This iron restriction is critical to preventing an excess of blood cell production and this is what is crucial to alleviate the severity of the disease in PV patients."

Patients with PV often develop iron deficiency when treated with venesection, but they are also advised against taking iron supplements as this would further accelerate the production of red blood cells in their body.

Dr. Bennett said targeting hepcidin could also help combat the iron deficiency symptoms faced by PV patients.

"This approach restricts iron access only to the bone marrow, without depleting iron from other organs, such as the liver," he said.

Silencing power

The research is being translated into Phase 1/2 clinical trials taking place across Australia, Malaysia and the United States.

The trials will use SLN124, a new drug developed by London-based Silence Therapeutics, in hopes of controlling hepcidin expression in PV patients for the first time.

Senior author and Head of WEHI's Population Health and Immunity Division, Professor Sant-Rayn Pasricha, said the trials involved PV patients receiving an injection every few weeks, in hopes of replacing their need for regular venesections.

"A treatment option like this would simplify long-term therapy for this disease for patients and the health care system," Professor Pasricha said.

SLN124 is a gene silencing therapy that works by inhibiting a gene responsible for hepcidin regulation in the liver. The clinical trials will investigate the effect of temporarily "silencing" this gene to increase production of hepcidin by the liver, which is expected to reduce disease severity.

"We recognized the opportunity to adapt an emerging clinical therapeutic initially designed for other hematological diseases such as b-thalassemia and apply it to polycythemia vera.

"To go from a concept to a clinical trial in less than four years is quite astounding.

"Our work has laid the essential foundation needed to hopefully transform patient care options for people with PV and provides unique insight that could lead to better understanding the disease."

Recruitment for the clinical trials has begun.

Landmark genome study

The study also uncovered a genetic link between a disorder that causes excess iron accumulation (hemochromatosis) and PV, made possible through WEHI's analysis of extensive population genetics databases including the UK Biobank.

The research team was able to leverage this data to conduct a genome-wide association study that analyzed data from 440 PV patients to further examine the role of iron in the blood cancer.

Professor Melanie Bahlo, laboratory head in WEHI's Population Health and Immunity Division, said having access to the UK Biobank was key to these discoveries.

Analysis of a second dataset, the Finnish FinnGen Biobank, confirmed the findings—highlighting the power of these databases to help formulate and test novel biological hypotheses.

"We were the first research team to use the UK Biobank to solely focus on PV samples, which led us to this powerful and novel insight about iron status and PV," she said. "This saw us further discovering that the genetic mutations which cause hemochromatosis are one of the strongest risk-factors for diagnosis of PV—an insight that will help the research field better understand this rare disease."

Dr. Victoria Jackson, a postdoc in Professor Bahlo's lab, performed the genetic analysis using a method called genome-wide association study.

More information: Cavan Bennett et al, Iron homeostasis governs erythroid phenotype in Polycythemia Vera, *Blood* (2023). DOI: 10.1182/blood.2022016779

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