

Research Reveals Opportunities to Better Address Blood Disorders Early in Life

Studies point to approaches—including a new gene therapy—that can set children on a healthier course with lifelong benefits.

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Researchers report significant progress toward improving access to effective interventions to address blood disorders and promote healthy blood cell functioning in four studies presented during the 65th American Society of Hematology (ASH) Annual Meeting and Exposition. The studies suggest new opportunities to act early in life to achieve lifelong benefits, including in children born with challenging disorders such as sickle cell disease (SCD) and hemophilia.

“This research really highlights the importance of early action and prevention,” said Sarah O’Brien, MD, of Nationwide Children’s Hospital. “From prenatal supplements to optimizing therapies, these findings show ways we can help our young patients be as healthy as possible, which can also improve outcomes with more complex therapies.”

The first two studies examine life-changing therapies for people living with SCD, an inherited blood disorder that affects the blood’s ability to carry oxygen, leading to organ damage and episodes of severe pain called vaso-occlusive crises. One provides new evidence that hydroxyurea, an oral medication widely available in the U.S. and other high-resource countries, is feasible, safe, and effective to administer at optimal doses in Africa, where many people with sickle cell currently lack access to treatment. The other study reports substantial and long-lasting benefits of a gene therapy for SCD, reflected not only in laboratory markers but in significant improvements in quality of life for people living with the disorder.

[Editor’s note: On December 7, 2023, the Food and Drug Administration [approved two new gene therapies](#) for sickle cell disease, Casgevy (the first CRISPR therapy) and Lyfgenia (lovo-cel).]

Two gene The third study sheds light on how the amount of folic acid, or folate, a developing fetus is exposed to in the womb can affect the system that maintains blood and immune cells in adulthood, with important implications for lifelong health.

The fourth study shows that a drug injected subcutaneously can help protect infants born with the

bleeding disorder hemophilia from serious complications such as intracranial bleeds. Avoiding such events at an early age can reduce children's chances of permanent brain and tissue damage and potentially set them up to receive the greatest possible benefit from other therapies later in life.

Lovo-cel gene therapy shows enduring results in preventing sickle cell pain crises

Abstract 1051: Efficacy, Safety, and Health-Related Quality of Life (HRQOL) in Patients with Sickle Cell Disease (SCD) Who Have Received Lovotibeglogene Autotemcel (Lovo-cel) Gene Therapy: Up to 60 Months of Follow-up

In the longest-running gene therapy trial for SCD to date, researchers report that a vast majority of patients have seen long-lasting, nearly complete resolution of vaso-occlusive events. With up to five years of follow-up and a median follow-up of three years, the new findings bolster evidence that lovo-cel is a safe and effective treatment for SCD.

"It is a truly transformative therapy," said Julie Kanter, MD, director of the Adult Sickle Cell Disease Program and professor of Medicine and Pediatrics at University of Alabama, Birmingham, and the study's lead author. "Using gene therapy through lovo-cel, we've been able to essentially rid individuals with SCD of vaso-occlusive events. It results in normal hemoglobin levels and people just feeling amazing."

SCD is caused by a gene that results in the production of abnormal hemoglobin, a protein in the red blood cells that carries oxygen. For lovo-cel therapy, stem cells are removed from a patient's bone marrow and a viral vector is used to add a gene to the stem cells that equips them to produce healthy hemoglobin. The modified stem cells are then returned to the bone marrow, where they manufacture blood cells with healthy hemoglobin.

Several other gene therapies for SCD are being tested in separate clinical trials. Lovo-cel is the longest running gene therapy trial for SCD to date and the only current trial to use a gene addition therapy rather than gene editing techniques to alter the stem cell genome.

The new findings include results from 34 pediatric and adult patients who completed lovo-cel therapy within the past 16 months to five years. Between six and 18 months following their lovo-cel infusion, 88.2% of the patients experienced no vaso-occlusive events at all and 94.1% experienced no severe vaso-occlusive events. By contrast, these patients suffered a median of three severe vaso-occlusive events per year for the two years before they enrolled in the trial.

A vast majority of patients showed significant amounts of new, non-sickle hemoglobin (HbAT87Q) induced by the gene therapy, resulting in marked improvements in total hemoglobin, Dr. Kanter reported.

"Even more exciting than the laboratory findings, many individuals have also reported significant improvements in terms of pain intensity, fatigue, and the degree to which pain interfered with daily life," said Dr. Kanter.

The process of administering lovo-cel requires patients to undergo an autologous stem cell transplant (a transplant that uses a patient's own stem cells instead of those from a donor) and uses conditioning chemotherapy to remove the old bone marrow and prepare the space for the new, modified stem cells. Side effects were common and consistent with conditioning chemotherapy including mouth sores and low blood counts. One patient was diagnosed with a blood cancer known as myelodysplastic syndrome. Scientists determined that the viral vector used for lovo-cel therapy did not cause the disorder; the patient also has not required any blood transfusions or experienced any vaso-occlusive events and continues to receive close monitoring.

Overall, the study provides strong evidence that lovo-cel is effective at the genetic level to produce healthy (non-sickled) hemoglobin, reduce hemolysis (cell breakage), improve total hemoglobin, and prevent vaso-occlusive events over an extended period while also improving patient quality of life; however, Dr. Kanter and team cautioned that longer-term data will be needed to determine whether it also helps to prevent stroke, kidney disease, and other longer-term complications of SCD.

To reduce health disparities commonly faced by people with SCD, Dr. Kanter added that it will also be important to work to address cost barriers and ensure equitable access to the therapy — as well as continuing care after patients receive it — if the therapy receives approval from the U.S. Food and Drug Administration.

"We don't know the long-term effects yet, so we need to make sure that the patients who get this gene therapy also receive ongoing care," said Dr. Kanter. "We also want to make sure that the centers that are performing these therapies really understand SCD and are equipped to take care of people with SCD for the best possible outcomes."

Dr. Kanter noted that the study has a relatively small sample size, was not randomized, and did not include people with severe renal disease, heart disease, or severe central nervous system vascular disease. The trial was funded by bluebird bio, developer of lovo-cel.

This abstract was presented by Julie Kanter of the University of Alabama, Birmingham in an oral presentation on Monday, December 11, 2023.

Extended use of hydroxyurea with optimal dosing found to be safe and effective in children with sickle cell anemia in Africa

Abstract 6: Hydroxyurea Dose Optimization Is Safe and Improves Outcomes for Children with Sickle Cell Anemia Living in Sub-Saharan Africa: The Reach Experience

Hydroxyurea is safe, well tolerated, and effective in Africa, according to the latest data from the Realizing Effectiveness Across Continents with Hydroxyurea (REACH) trial. REACH is the largest trial to test hydroxyurea in children anywhere in the world and among the first to test its feasibility in real-world settings in Africa, where children with sickle cell anemia face additional health risks such as malnutrition and malaria that are less prevalent elsewhere.

The new data align with findings reported earlier in the study and, now with an average follow-up of over seven years, increase confidence that hydroxyurea treatment can be feasibly maintained in African settings with good safety and efficacy in the long term. In addition, the study underscores the importance of achieving the optimal dose of hydroxyurea, as higher doses lead to the best clinical responses.

“It’s really exciting to see that the optimal dose is safe and effective,” said Banu Aygun, MD, Cohen Children’s Medical Center of New York, and the study’s lead author. “It suggests that we should advocate for giving the best dose to children living in Africa just like we are doing here in the United States.”

Newborns are routinely screened for SCD in the United States, where there are currently about 100,000 affected individuals, most of whom have access to treatments such as hydroxyurea, which reduces SCD complications by increasing the production of fetal hemoglobin. In Africa, where it is estimated that over 300,000 babies are born with sickle cell each year, newborn screening programs are just beginning to be established and the vast majority of children do not have access to hydroxyurea treatment.

For the REACH trial, researchers worked with local partners in Angola, the Democratic Republic of Congo, Kenya, and Uganda to administer hydroxyurea to a total of 606 children with a genetic subtype of SCD known as sickle cell anemia, 86% of whom still remain on treatment an average of over seven years later.

Participants received a low fixed dose of 15 to 20 mg/kg/day initially to ensure safety. Once safety was established, the dosing was raised and then further optimized to allow each patient to receive the highest dose they could tolerate safely. After this optimization process, the average dose reached about 27.5 mg/kg/day, which is similar to the optimal dosage of 25 to 30 mg/kg/day that is standard in the United States.

These extended REACH results show both safety and strong efficacy, especially when comparing the optimized dose with the lower initial fixed dose. Laboratory responses including various measures of hemoglobin content in the blood improved with increasing dosage, while the rate of events including vaso-occlusive episodes, acute chest syndrome, enlargement of the spleen, stroke, transfusions, malaria, non-malarial infections, and deaths decreased. There were few safety concerns and a low overall rate of dose-related toxicities.

Researchers say hydroxyurea is well suited for use in Africa because it is a daily pill that does not require refrigeration, is relatively inexpensive, and has a long track record of benefits. However, the feasibility of its implementation in Africa was uncertain until this study because of concerns about cost, how well the treatment would work in populations facing risks that have not been previously studied such as malnutrition and high rates of malaria, and whether issues such as lack of transportation, language barriers, and political instability would hinder families’ ability to access clinics.

Based on the results, researchers say there is now good evidence that hydroxyurea treatment at

optimal dosing is feasible and beneficial for children living with sickle cell anemia in Africa.

“Many newborn screening programs are coming out [now], and we know for newborn screening programs, it’s not enough to diagnose a condition if you can’t tie it to a treatment,” said Dr. Aygun. “If we are diagnosing children with sickle cell anemia, we have to be able to offer hydroxyurea to them.”

Banu Aygun of Cohen Children’s Medical Center presented this study in the Plenary Scientific Session on Sunday, December 10, 2023).

Researchers trace lifelong impacts of folate deficiency during early development

[Abstract 5](#): Metabolic Programming of Hematopoietic Stem Cell Function By Prenatal Folate

For decades, pregnant women have been advised to consume enough of the B-vitamin folic acid, or folate, to prevent neural tube defects in their babies, and many foods in the U.S. are fortified with folate for this reason. However, there has been little understanding of how folic acid might affect prenatal development in other ways. Now, a new study conducted in mice has uncovered some of the mechanisms by which exposure to too little — or too much — folate in the womb can affect a person’s health and susceptibility to disease into adulthood.

The study examines the relationship between prenatal folate availability and metabolic programming of hematopoietic, or blood, stem cells (HSCs), the stem cells that give rise to all blood and immune cells in the adult body. When functioning properly, HSCs ensure the body has the right types and amounts of blood and immune cells.

“Our study shows how manipulation of nutrients during early development can shape the function of the adult blood system by programming blood stem cells during development,” said Brian Krum, MSc, a PhD student at the University of Utah, and the study’s lead author. “These changes persist into adulthood where they have permanent effects on the hematopoietic system and also potentially affect immune function and disease risk.”

Previous studies have shown that folate helps regulate red blood cell production; in adults, low-circulating folate can cause anemia. The new study is the first to examine how folate levels in a pregnant mother affect HSCs in her children. The results reveal that prenatal folate exposure can affect HSCs and their function into adulthood.

The researchers assessed HSC function in the offspring of mice that were fed diets that were folate deficient, folate sufficient, or folate supplemented during pregnancy. The results showed that HSCs from adult mice that were exposed to folate deficiency during fetal development had poorer performance in producing all types of blood and immune cells, while those that were exposed to excess folate during development overproduced all the same blood and immune cells.

Tracing the metabolic pathways involved, the researchers found evidence that mitochondrial dysfunction was instrumental in driving the effects of folate deficiency on HSCs. Dysregulation of mitochondrial metabolism was evident in HSCs during fetal development and persisted into adult

HSCs, suggesting that sustained metabolic defects are a key driver of the underlying dysfunction.

For pregnant women, researchers said the findings underscore the need to address folate deficiency, which is common in lower-resourced countries where people may not have access to enough folate-rich foods. While folate deficiency is rare in countries like the U.S. where food is fortified with folate and folic acid supplements are often taken during pregnancy, Krum noted that consuming excess folate may also have implications for blood and immune function.

The study findings are also relevant to understanding the interactions between nutrition and anti-folate chemotherapy drugs. Researchers suggested future studies illustrating the metabolic aspects of HSC programming by folate might help identify novel pathways and targets to more selectively target folate metabolism in blood cancers, particularly pediatric leukemias, in order to achieve the best therapeutic benefit while minimizing toxicities.

Brian Krum of the University of Utah presented this study during the Plenary Scientific Session on Sunday, December 10, 2023).

Emicizumab found safe and effective for preventing bleeding in infants with Hemophilia A

[Abstract 505](#): Emicizumab Prophylaxis in Infants with Severe Hemophilia A without Factor VIII Inhibitors: Results from the Primary Analysis of the HAVEN 7 Study

In a new study, infants with severe hemophilia A who started receiving emicizumab in the first few months of life experienced few bleeding events, no other serious hemophilia complications, and no serious treatment-related adverse events. Researchers say the results offer reassurance that this hemophilia drug, which was previously tested mostly in older children and adults, is safe and effective for use in infants too.

The drug could fill a significant gap for babies born with hemophilia A, who generally cannot receive factor VIII infusions to replace the clotting agent that their bodies do not make naturally, due to challenges with administering regular intravenous infusions in young infants (including challenges with venous access and the need for central venous access devices). Without factor VIII infusions or other therapies, these babies can be vulnerable to uncontrolled bleeding and damage to joints and organs, including bleeding in the brain.

“Emicizumab proved to be highly efficacious in these infants in preventing all bleeds, traumatic bleeds, and spontaneous bleeding, and it was well tolerated,” said Steven Pipe, MD, of the University of Michigan, the study’s lead author. “I think this is going to be adopted broadly [as a prophylactic agent in infants].”

Factor VIII infusions are a mainstay of hemophilia A treatment, particularly for stemming severe bleeding or controlling bleeding during surgery. However, these infusions can become less effective if patients develop antibodies that inhibit factor VIII, something that grows more likely

with increased exposure to factor VIII.

Emicizumab is an effective prophylactic therapy even in the presence of factor VIII inhibitors, Dr. Pipe explained. Since its approval as a first-line hemophilia therapy in 2017, emicizumab has been increasingly adopted as a prophylactic drug to prevent bleeding and reduce the number of factor VIII infusions patients require.

Until now, there has been little data on the use of emicizumab in young babies. For the study, researchers administered the drug to 55 infants with hemophilia A starting at a median age of four months and continuing for a median of just under two years and a minimum of one year. After an initial loading period of four weekly injections, parents administered the drug at home via subcutaneous injection every two weeks.

Throughout the study, over half of the study participants (54.5%) had no bleeds requiring treatment. All treated bleeding events were related to trauma such as scrapes and falls; no participants had bleeding in the brain or spontaneous bleeds requiring treatment. Laboratory tests showed that most participants were able to maintain therapeutic concentrations of the study drug in their bodies and none developed antidrug antibodies.

Adverse events such as fevers and infections were common, which was expected given that infants frequently experience minor illnesses. The only adverse events that were considered treatment-related were low-grade reactions (localized redness of the skin) at the injection site, which occurred in 16.4% of participants and were temporary, said Dr. Pipe.

Researchers noted that more research will be needed to gauge any long-term effects of emicizumab use in babies, including whether it helps reduce the use of factor VIII and consequently the development of factor VIII inhibitors. In the meantime, Dr. Pipe suggested that emicizumab represents a good prophylactic option for babies, especially during the first year when administering factor VIII as a prophylactic therapy is often not feasible.

“Many people would call this a game-changer as far as clinical practice is concerned,” said Dr. Pipe. “If you’re a parent of an infant with hemophilia, to have a therapeutic option that you can get your baby started on as soon as possible just provides such reassurance for the family.”

Steven Pipe, University of Michigan, presented this study in an oral presentation on Sunday, Dec. 10, 2023).

This [news release](#) was published by the American Society of Hematology on December 9, 2023.

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