VIEWPOINT

SCIENTIFIC DISCOVERY AND THE FUTURE OF MEDICINE

Accelerating the Science of SCD Therapies—Is a Cure Possible?

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Nearly 7 decades have passed since seminal studies of hemoglobin led to the characterization of sickle cell anemia as the first defined molecular disease. These foundational insights into sickle cell disease (SCD) initiated an exciting era of medicine that has substantially expanded the understanding of the molecular basis of thousands of disorders over the ensuing years. The field of molecular medicine is now at a pivotal moment in its history, a time when scientific capabilities to read, edit, and reprogram the human genetic code for therapeutic approaches are within reach. The rapid pace of innovation in emerging technologies of gene editing and translational research suggest that it is time to accelerate curative therapies for the first defined molecular disease.

More than 100 years have passed since *Archives of Internal Medicine* (now *JAMA Internal Medicine*) published Herrick's description of misshapen red cells in a Grenadan medical student.[1] In hindsight, it is now understood how this "puzzling" clinical observation in an individual of African ancestry fits within the current "central dogma" of molecular medicine: DNA-RNA-protein-disease. Sickle cell disease is a hemolytic anemia caused by a mutation in the β globin subunit of adult hemoglobin (HbA) that substitutes valine for glutamic acid at position 6. When deoxygenated, HbS polymerizes, rendering the red cell rigid, viscous, and abnormally adherent to the capillary endothelium. This impedes blood flow in the microcirculation, causing ischemia and microinfarcts that lead to painful crises, strokes, renal failure, retinopathy, and myriad end-organ injuries.

Although the discovery of the molecular basis of SCD was a triumphant milestone in molecular medicine,[2] it is still a tragic truth that in the absence of access to treatments, infants born with SCD are unlikely to live to adulthood in many parts of the world. Over the past 4 decades, advances such as penicillin prophylaxis, standardized vaccine schedules, transfusion support, and hydroxyurea therapy have significantly extended life expectancy for those with SCD. Nevertheless, many individuals with SCD in the United States still lack a patient-centered medical home with access to evidence-based care that optimizes health outcomes.

Within the current therapeutic armamentarium, hydroxyurea is the first successful treatment strategy to address the molecular basis of SCD through the induction of a partial increase in the production of fetal hemoglobin (HbF). Fetal hemoglobin does not sickle and offers the added benefit of inhibiting deoxygenated-HbS polymerization. Approved by the US Food and Drug Administration (FDA) in the late 1980s, hydroxyurea prolongs patient survival and reduces painful crises and acute chest syndrome. Challenges and adverse effects related to hydroxyurea use have accentuated the need for further research to catalyze a new generation of SCD treatments.

Recent studies have uncovered many new dimensions to the pathophysiology of SCD both within and beyond the red cell. The damage inflicted on the vasculature by the pathological adherence of sickle red cells provokes inflammation, vasoconstriction, oxidative damage, and prothrombotic phenomena. This vasculopathy is a key driver of the disease state and mediates many of the complications. New insights about the molecular signals governing fetal to adult hemoglobin switching provide many new therapeutic targets.

Clinical studies resulting from this progress in basic and translational science are yielding novel therapeutics. Multiple agents are in clinical trials with a variety of targets such as reducing HbS sickling by modifying its deoxygenation, increasing HbF by manipulating the complex epigenetic mechanisms that silence gene expression, and targeting the selectins mediating endothelial adhesion (eg, a recent P-selectin inhibitor was granted Breakthrough Therapy designation by the FDA to reduce vaso-occlusive crises).[3,4] Many trials are underway to address other downstream pathologies including nitric oxide scavenging and vasoconstriction due to free hemoglobin S released during hemolysis, the hypercoagulable state arising from endothelial damage, and antioxidants that detoxify by-products of inflammation.[3] For example, L-glutamine is a 2017 FDA-approved drug that mitigates oxidative stress within erythrocytes and leads to reduced vaso-occlusive crises and incidence of acute chest syndrome. This heightened refocus on therapies for SCD reflects advances in the understanding of its pathobiology and holds promise for expanding treatment options for patients.

The recent wave of emerging SCD drug treatments is an exciting advance, yet most of these agents require lifelong administration, have uncertain long-term adverse consequences, and fall short of altering natural history. Recent advances in gene therapy and gene editing technologies make the ultimate goal of durable curative therapies possible and justify the pursuit of clinical studies of these modalities.

Over the past 2 decades, allogeneic hematopoietic stem cell transplants (HSCTs) have been a viable curative approach for a limited number of patients with SCD by replacing the patient's blood-forming stem cells with stem cells from a normal donor. For example, a recent study demonstrated that children with SCD who required a chronic transfusion because of elevated transcranial Doppler (TCD) velocities, a major risk factor for stroke, who underwent matched sibling donor HSCT

(n = 32) had significantly lower TCD velocity at 1 year than a matched cohort of children (n = 35) who did not undergo transplant.[5]

However, major limitations preclude widespread applicability, including a paucity of matched donors, high cost, and the need for highly sophisticated tertiary care centers capable of performing the procedure. Acute mortality (5%-10%) and the risk of late effects, such as graft-vs-host disease, prolonged immunosuppression, sterility, secondary malignancies, or late graft rejection, are also impediments to achieving a scalable approach to a cure. Newer minitransplant regimens are better tolerated but at the potential expense of less complete or durable replacement of the SCD stem cells. Currently available therapies are thus hampered by unpredictable efficacy, toxicity, and limited applicability.

The goal of gene therapy for SCD is to insert a gene that codes for a desired RNA or protein product into the patient's own stem cells and to have it expressed durably at levels sufficient to overcome the levels of sickle hemoglobin. Two specific strategies are being tested: replacing the mutated β-globin gene and disrupting the expression of the BCL11a transcription factor that represses HbF production. The procedure involves an autologous HSCT whereby the patient's own stem cells are mobilized, collected by apheresis, and modified by a viral vector that delivers the new gene. In 2017, a patient treated with a lentiviral vector encoding a nonsickling β-globin experienced a progressive increase in HbA production that stabilized over time and resulted in transfusion independence.[6]

Gene editing leverages endonucleases to make permanent modifications to host DNA by producing targeted double-stranded breaks that allow for the insertion of the desired change in the DNA sequence. The majority of gene editing research in SCD currently uses CRISPR/Cas9 (or related nucleases) and guide RNA sequences to target specific gene segments. Related strategies include the use of either zinc-finger nucleases or transcription activator-like effector nucleases (TALENs) that use peptides to bind specific trinucleotide and mononucleotide sequences, respectively.[7] Currently, there is 1 US phase 1 clinical trial for gene editing in SCD that is open for enrollment.

Gene-based therapies circumvent some, but not all, of the disadvantages of allogeneic HSCT. There is no need for a donor and no risk of graft-vs-host disease. However, all regimens currently under study require an autologous stem cell transplant. Each patient's own stem cells must be mobilized and harvested for ex vivo transfection by the correcting gene. Studies are underway to optimize stem cell mobilization and harvesting strategies. Developing noncytotoxic regimens that partially ablate ("condition") the bone marrow to create a niche for the therapeutically engineered stem cells is of paramount importance. Busulfan, frequently used in conditioning regimens, causes infertility. Further research is needed to develop less toxic conditioning regimens. If these high-cost curative genetic therapies prove to be safe and effective, it may be important to assess the long-term cost benefit of these one-time curative therapies vs the ongoing expenses of lifelong management with the current drugs for SCD.

Perhaps the most ambitious vision is to further accelerate innovative technologies that will make it feasible to pursue in vivo gene editing that obviates the need for ex vivo manipulation and bone marrow transplant. This bold, ambitious vision anticipates in vivo gene editing technology platforms capable of targeted delivery to hematopoietic stem cells in situ. If advances in emerging technologies such as cell-directed nanoparticles make this approach possible, it is conceivable that in vivo gene editing might eventually be feasible to administer as a "same-day hospital" protocol that could be amenable to broad deployment at scale, including more resource-limited settings. Ultimately, the hope of this provocative concept is to develop curative therapies with either small molecules or genetic therapy interventions that will transform the lives of patients with SCD throughout the world.

As the field of molecular medicine races ahead in its capacity to read, edit, and reprogram the human genome, judicious deliberation about safety (eg, off-target effects) and ethical, legal, and social implications of these new technologies is paramount. Engagement of individuals living with SCD and their families as partners in this research effort must soberly acknowledge the history of mistreatment of minority groups in research and the legacy of mistrust that lingers as an aftermath.[8] The National Institutes of Health/National Heart, Lung, and Blood Institute's Cure Sickle Cell Initiative seeks to create an ecosystem of partners that links the SCD patient community with academia, federal agencies, pharmaceutical and biotechnology companies, and clinicians. This effort strives to include patients and advocates at every stage and level of activity to ensure a patient-centered approach.

Success requires perseverance to overcome the many challenging hurdles in the development of transformative treatments for SCD. There is optimism for envisioning a hopeful future in which molecular medicine will finally fulfill the dream of every family affected by SCD: a child born with sickle cell disease who enjoys a pain-free, stroke-free journey into adulthood, and enjoys…a normal life.

ARTICLE INFORMATION

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