Sickle Cell Disease and Fetal Hemoglobin

Sickle cell disease (SCD) is a genetically inherited abnormality of the β-hemoglobin gene, referred to as hemoglobin S, affecting millions of people worldwide. Despite evidence that child death rates from SCD are declining, the relative burden of child morbidity and disability will increase in the coming decades. Projections by Piel *et al.*[1] have shown a 30% increase in SCD births by 2050, which underscores the need to develop novel and effective therapies. However, lack of suitable tools to test promising experimental drug therapies hamper further progress.

Under low-oxygen conditions and/or pH, hemoglobin S polymerizes, forming sickle-shaped rigid cells with low survivability rates.[2] These dysfunctional oxygen-carrying cells are sticky and are easily trapped within small vessels, leading to vaso-occlusion, intravascular hemolysis and tissue damage in major organs. High recurrent infections, anemia, excruciating pain in extremities, leg ulcers, priapism, organ damage and stroke are among the common characteristics of this disease – events that lead to a poor quality of life, constant transfusions and frequent hospitalization. Treatment options for SCD are nonspecific and very limited. These include bone marrow transplantation, pain medication, blood transfusions and/or two US Food and Drug Administration (FDA)-approved drug treatment options, namely, L-glutamine oral powder (Endari) and hydroxyurea (hydroxycarbamide). In this issue of the Saudi Journal of Medicine and Medical Sciences, Mozeleski *et al.*[3] provide an important and compelling rationale to develop a novel approach to more accurately and precisely quantify cellular levels of hemoglobin F (HbF).

WHY TARGET HEMOGLOBIN F?

In an otherwise healthy human fetus, HbF is present during the final months of development, representing about 75% of the total hemoglobin until the newborn is 7–8 months, when HbF is significantly reduced to 1%–2% of total hemoglobin.[2] Complications of SCD are not apparent in neonates and are mainly observed when HbF levels decrease and adult forms of hemoglobin rise.

HbF levels correlate with enhanced red cell survival, reduced hemolysis and increased absolute reticulocyte count, an index of the bone marrow's response to hemolysis.[4] However, HbF is heterogeneously distributed among sickle red cells and maybe as high as 30% due to genetic factors, the number of cells expressing HbF (F-cells) and the amount of HbF per F-cell. Evidence suggests that within the F-cell population, cells with higher HbF levels survive longer and are associated with improved anemia and reduced organ damage.[4] The Cooperative Study of Sickle Cell Disease reported a significant reduction in clinical severity and mortality in SCD patients and suggested that therapeutic agents capable of inducing HbF synthesis would lead to improved clinical outcomes.[5] Assays to accurately and more precisely measure the intracellular distribution of HbF levels may lead to significant advances in therapeutic development and prognosis, as proposed by Mozeleski *et al.*[3] As the genetic and pathophysiological understanding of HbF regulation improves, these assays will become more important.[6,7]

Gardner *et al.*[8] reported the development of a genetic marker in which seven common gene variants within *BCL11A*, *HMIP-2A*, *HMIP-2B* and *Xmn1-HBG2* in the β-globin locus were grouped to create a single genetic quantitative variable for HbF: *g(HbF)*. Evidence suggests that *g(HbF)* is associated with HbF levels determined using the Bio-Rad Variant II and markers of disease severity.[9] Mozeleski *et al.*[3] posit that determination of HbF/F-cell measures would improve the prognostic value of *g(HbF)*.

Hydroxyurea increases HbF expression and reduces hematological complications, including painful crises, acute chest syndrome and transfusion rates, with limited side effects. A multicenter study of hydroxyurea showed that use of hydroxyurea reduced painful crises by about 40%.[10] In addition, hydroxyurea recently received FDA approval for use in SCD children aged ≥2 years with moderate to severe painful crises, and thus its use is expected to increase worldwide.[11]

STATE-OF-THE-ART AND LIMITATIONS OF CURRENT TECHNIQUES

High-performance liquid chromatography is the gold standard assay for HbF detection and analyses. It provides measures of HbF as a percent of total hemoglobin, but does not provide a full cellular distribution. Imaging flow cytometry is a useful tool for HbF analysis but is not suitable for quick clinical diagnostics. Standard flow

cytometry may be used to develop a test assay to provide the percentage, level and distribution of F-cells. Other measures used to provide qualitative assessments of HbF include hemoglobin electrophoresis, isoelectric focusing and/or capillary electrophoresis.

In conclusion, precise and quantitative measures of cellular HbF levels will improve diagnosis and prognosis and increase our understanding of SCD's pathophysiology. Successful development of Mozeleski *el al.*'s[3] assay could lead to an improved ability to more precisely measure HbF/F-cell levels, and thus properly evaluate new and current therapies in SCD worldwide.

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