New agents for sickle cell disease: patient perceptions of benefit in the real world

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Sickle cell disease (SCD) is one of the most important monogeneic diseases in the world, causing significant morbidity and mortality and consuming substantial healthcare resources.[1] SCD results from a single amino acid substitution in the β-globin chain, leading to sickle hemoglobin (HbS). In oxygen-limited settings, HbS forms polymers that lead to the characteristic sickle-shaped erythrocytes and also to changes in the erythrocyte membrane. The pathological features of SCD result from a combination of vaso-occlusive events precipitated both by abnormal erythrocyte morphology and the increased expression of adhesion molecules on its outer membrane; accelerated hemolysis that can deplete nitric oxide and that leads to anemia; and a high level of endogenous inflammatory activation associated with repeated ischemia/reperfusion cycles, themselves precipitated by vaso-occlusion.[2]

Hydroxyurea, the first-line and indeed only approved therapy for SCD for some 20 years, was approved in 1998.[3] Hydroxyurea upregulates δ-globin production, increasing intracellular levels of hemoglobin F which in turn decreases polymerization of HbS. Hydroxyurea therapy decreases the frequency of painful vaso-occlusive crises, blood transfusions, and hospital admissions.[4]

However, there are factors that result in underutilization of hydroxyurea in SCD.[5] Although frequently prescribed, there is a high incidence of discontinuation due to side effects (24.6% in one recent report[4]) but also due to patient perception of ineffectiveness (16.4%[4]). In the last few years, three new agents have been approved for the treatment of SCD, each of which addresses a different element of SCD pathophysiology[6]: L-glutamine, which reduces oxidative stress in SCD by increasing erythrocyte nicotinamide adenine levels; crizanlizumab, a competitive inhibitor of P-selectin that decreases sickle erythrocyte adhesion during vaso-oclusive crises; and voxelotor, which increases hemoglobin oxygen affinity and prevents HbS polymerization.[7 8]

In a paper in this issue of *JIM*, Idowu and colleagues discuss patient perception of the treatment benefit for 23 consecutive patients with SCD (21 homozygous SCD (HbSS), 2 sickle-β^0 thalassemia) received from voxelotor.[9] All had significant ongoing hemolysis resulting in anemia and had evidence of organ dysfunction. They were evaluated using two separate scales that assessed the global impression of change in patient status from the perspective of the clinician and of the patient, respectively. Most patients reported a perception of substantial clinical improvement. Interestingly, this did not correlate entirely with the changes in hemoglobin concentration, since some patients reported improvement with stable or even worsened anemia, although most patients had evidence of improved hemoglobin concentrations and decreased hemolysis.

This study did not include patients who were unable to have voxelotor covered by a payer. This is a significant challenge in patients treated with new agents: in another recent real-world cohort study of voxelotor in SCD, approximately one-third of patients for whom it was prescribed never took voxelotor, due to problems completing required paperwork (41%), disapproval by insurance (18%), or high copays (5%).[10]

Studies like this report by Idowu and colleagues advance clinical practice by recognizing the importance of the perceptions of the two primary partners in patient care: the clinicians and the patients themselves.

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