EDITORIALS

Hydroxyurea — An Essential Medicine for Sickle Cell Disease in Africa

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Higher levels of fetal hemoglobin (HbF) ameliorate the clinical course of sickle cell disease. Hydroxyurea, an inhibitor of the enzyme ribonucleoside diphosphate reductase, increases HbF synthesis by erythroid cells (Fig. 1). More than 20 years ago, a major clinical trial of hydroxyurea in the management of sickle cell disease proved successful.[1] Subsequent studies, including eight randomized, controlled trials, that have involved adults, children, and specific clinical situations all showed benefit from hydroxyurea,[2] with particular effects on pain reduction, prolonged survival, improvement in quality of life, and recently, prevention of end-organ damage. Hydroxyurea is now recognized in national and international guidelines as a standard of care for patients with sickle cell disease.[3] Hydroxyurea has been used in many parts of the world, and there is "no theoretical or empirical reason why hydroxyurea should be less beneficial or less safe for African patients compared to patients elsewhere."[4] However, it is one thing to assume that hydroxyurea is going to be safe and efficacious in Africa; it is another to have evidence.

In this issue of the *Journal*, Tshilolo et al.[5] provide this evidence, and they also dispel the myth that clinical trials cannot be performed in Africa. Their article gives a detailed account of the benefits of hydroxyurea in children with sickle cell disease attending clinics in four African countries — Angola, Democratic Republic of Congo, Kenya, and Uganda — and it highlights the potential of professional partnerships on a global scale. In a cohort of 600 children who were followed for 3 years, the authors documented an increase in the HbF level, an increase in the hemoglobin level, a decrease in neutrophil counts, and a decrease in the number of painful crises. These results were largely expected (Fig. 1) but are no less elating. The trial did not have a placebo group (appropriately, in our view, since hydroxyurea is already the standard of care), and when dose escalation to the maximum tolerated dose was included, a gradual positive trend was seen in several clinicohematologic variables as escalation progressed. One unexpected finding was a decrease in the incidence of episodes of malaria, which could be explained by better-than-average antimalarial measures, some recovery of splenic function, or direct inhibition of *Plasmodium falciparum* growth. At any rate, this finding ought to dispel concerns about the use of hydroxyurea in areas where malaria is endemic.[6]

Tshilolo et al. decided to recruit children to the trial without any clinically related selection, in agreement with a 2014 expert panel that recommended hydroxyurea treatment in all infants and children with sickle cell disease who are 9 months of age or older, even if they were asymptomatic.[3] The results of the trial suggest that hydroxyurea should be given to all patients with sickle cell disease, on the assumption that it is widely available. However, if supplies are limited, triaging for hydroxyurea administration those patients who have more complications or who are at higher risk may be unavoidable. With regard to using a fixed dose or the maximum tolerated dose, under real-life conditions, as opposed to the more protected setting of a trial, one will always have to balance the risk of toxic effects against the benefit of a higher dose.

The term "molecular disease" was first coined

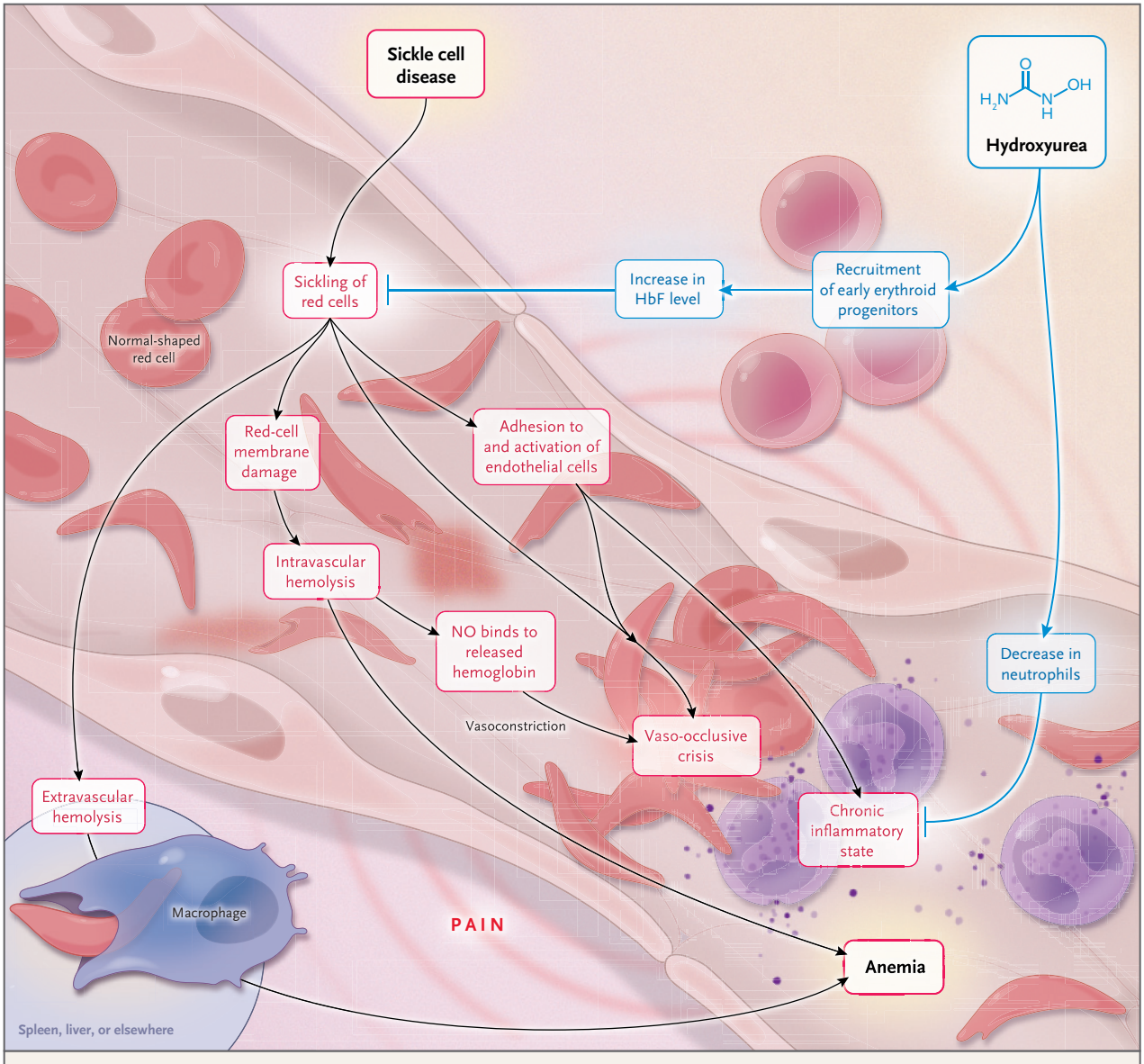

Figure 1. Modification of the Pathophysiology of Sickle Cell Disease by Hydroxyurea.

All the manifestations of sickle cell disease depend, directly or indirectly, on sickling, which in turn is produced, as red cells deliver oxygen to tissues, by the polymerization of deoxyhemoglobin S. Sickled red cells may become stuck in capillaries and, by jamming small vessels, may cause vaso-occlusion and consequent pain crises. Sickled red cells may undergo lysis within the bloodstream (intravascular hemolysis), whereby hemoglobin released in the plasma will bind nitric oxide (NO), resulting in vasoconstriction that will further favor vaso-occlusion. Sickled red cells will also be phagocytosed by macrophages (extravascular hemolysis); together with intravascular hemolysis, this causes anemia, often severe. Sickled red cells will also adhere to the endothelium, causing a chronic inflammatory state that is associated with neutrophil leukocytosis. The main action of hydroxyurea is to cause an increase in the intracellular concentration of fetal hemoglobin (HbF), which interferes with the deoxyhemoglobin S polymer formation, reducing the rate of sickling. Through this mechanism, hydroxyurea affects the very source of all the pathologic features of sickle cell disease. In addition, hydroxyurea lowers the neutrophil count, thus reducing the chronic inflammatory state.

for sickle cell disease, and subsequent genomics research[7] has helped us to understand further its molecular pathophysiology.[8] Sickle cell disease can be cured by allogeneic bone marrow transplantation[9] and very recently by a remarkably successful gene-therapy protocol.[10] However, even in

Europe and the United States, only a small minority of patients with sickle cell disease undergo bone marrow transplantation.[11] The burden of sickle cell disease is greatest in Africa, where it is recognized as a public health priority and where early mortality may reach 90%, especially when people live in poverty. Patients with sickle cell disease in Africa ought to have access to the most advanced methods of intervention, but this should go hand in hand with the availability of hydroxyurea therapy on a wide scale.

To this end, a major limiting factor has been affordability. Today in a pharmacy in Tanzania, the mean price for a typical daily dose of hydroxyurea is approximately $1.20 — not a small sum, if you need it every day for a lifetime. Free health care for all is a desirable goal. Until it is attained, we need to explore new avenues for reducing prices and to do so now — for instance, local compounding of galenic hydroxyurea by qualified pharmacies or production of the drug by the local pharmaceutical industry.

Another limiting factor may have been in the mind of some that there was no positive evidence that hydroxyurea therapy was safe and effective in Africa. Given the landmark article by Tshilolo et al., any such doubt must be discarded. It is clear that providing hydroxyurea therapy to patients with sickle cell disease in Africa is no longer just a desirable option but an immediately realistic obligation. Hydroxyurea should be on the List of Essential Medicines in all countries in Africa.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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Open or Endoscopic Vein Harvesting for Coronary-Artery Bypass Grafting

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Coronary-artery bypass grafting (CABG) is the most common cardiac surgical procedure performed worldwide, with more than 200,000 of the procedures performed annually in the United States alone.[1] Amidst several advances, the use of saphenous-vein grafts for bypass grafting remains common[2,3]: more than 90% of CABG procedures are performed with saphenous-vein grafts. However, two recalcitrant issues with saphenous-vein grafts persist — early graft failure and harvest-site complications.

Traditionally, harvesting of the greater saphenous vein involves a long incision along the medial part of the lower leg or thigh. This approach is associated with significant wound complications, including infection, delayed healing, and postoperative pain,[4] which often extend the length of stay in the hospital or result in a need for home care nursing support for wound dressing and surveillance.

Minimally invasive endoscopic harvesting of saphenous-vein grafts was introduced in the mid-