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Is low dose hydroxyurea the solution to the global epidemic of sickle cell disease?

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Sickle cell disease is a chronic illness that has been neglected in regions with limited health care resources. Unlike obesity, cardiovascular disease, hypertension, diabetes mellitus, and malignancies, which are now epidemic in lower and middle income countries and for which regions-specific data are emerging, the vast majority of cases of sickle cell disease occur in Africa and India. However, most of the research is performed for patients in the United States and Europe, higher income countries with <1% of the new cases of sickle cell disease. [1]

The Global Burden of Disease Study estimated that 176,200 people died worldwide from sickle cell disease in 2013 and that sickle cell disease was responsible for more years of life lost than typhoid fever, leukemia, or measles. [2] Most people with sickle cell disease in Africa and India probably die during early childhood from common and potentially preventable infections, such as malaria and pneumococcus. [3] Their predisposition and increased risk of mortality from these infections is unrecognized, because newborn screening for sickle cell disease is not available. Even when a diagnosis of sickle cell disease is made, comprehensive care for the disease is available for few and is limited to prophylaxis for infectious complications and treatment of some acute and chronic complications, but disease modifying therapies, such as hydroxyurea, chronic transfusion of sickle negative blood, or hematopoietic stem cell transplantation are generally not. Hydroxyurea is the least complicated and expensive of these therapies, but the standard approach of dose escalation and regular laboratory monitoring for hematological toxicity is not feasible in areas with limited health care resources. Svarch and colleagues in the Central America and the Caribbean pioneered the use of fixed weight-based dosing of hydroxyurea to treat children with sickle cell anemia. They reported an 80 percent reduction in the median number of hospitalizations and a greater than 70 percent reduction in acute painful

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events after the initiation of hydroxyurea in 52 children; they noted no hematological toxicity although only total white blood cell count was measured. [4]

The results presented by Dr. Dehury and colleagues address several of the important gaps in our knowledge about hydroxyurea for the treatment of sickle cell disease, including its use for patients with HbSβ^+ thalassemia in an area with limited health care resources and lower weight-based dosing without dose escalation. [5] Hydroxyurea has been shown to decrease the frequency of hospitalization, acute painful events, transfusion, acute chest syndrome, and mortality in Greek patients with sickle β-thalassemia treated in a prospective non-randomized cohort study. This study started participants on hydroxyurea at 20 mg/kg/day and the mean final dose was 17.5 mg/day. [6] Dr. Dehury and colleagues studied both the safety and efficacy of a low fixed weighted-based dose of hydroxyurea (average daily dose of 10 mg/kg as 500 mg capsules) to treat the most common genotype of sickle β-thalassemia (IVS1–5(G—>C) in India. [7] Nearly two thirds of the over 300 patients at their center with this genotype (97% of their patients with HbSβ^+ thalassemia) started hydroxyurea at 10 mg/kg/day. They reported results from the 37 children and 67 adults that received hydroxyurea for at least 2 years and demonstrated a remarkable decrease in the rates of acute painful events, hospitalization, and blood transfusions in both the children and adults. This clinical improvement occurred with a relatively small mean increase in fetal hemoglobin (from 16 before hydroxyurea to 20 percent with hydroxyurea) and mean decrease in the absolute neutrophil count (from 5,500 to 4,000/ul in children and 5,232 to 4,400/ul in adults). At this low dose, toxicities were uncommon. Laboratory testing every 3 months identified myelotoxicity in one child (absolute neutrophil count < 2,500/ul) and thrombocytopenia (platelets < 80,000/ul) in 4 adults that resolved after halting hydroxyurea temporarily. No hepatic, renal, cutaneous, or allergic adverse effects occurred. Reproductive toxicity was assessed by semen analysis in 17 men before and during treatment with hydroxyurea. Three had oligospermia and one azoospermia before treatment. In one participant pre-existing oligospermia worsened and one patient with normal sperm parameters developed oligospermia and abnormal sperm morphology after 6 months of treatment. These parameters returned to their baseline values 8 weeks after hydroxyurea was temporarily discontinued. These data on semen quality with low-dose hydroxyurea are limited, but overall reassuring. This is in contrast to some reports of a high prevalence of oligospermia and azoospermia in adults treated with hydroxyurea at higher doses. [8]

These results reported by Dr. Dehury and colleagues complement the authors' prior demonstration that 10 mg/kg/day of hydroxyurea decreased the frequency of acute painful events and transfusion in their patients with both sickle cell anemia and hemoglobin SD-Punjab disease. [9,10] Hydroxyurea used at this dose in this population has infrequent toxicity and probably can be safely administered without regular monitoring for hematological toxicity. Additional studies of hydroxyurea in areas with limited health care resources are ongoing and include the use of hydroxyurea for the prevention of stroke (Nigeria NCT01801423) and to prevent sickle cell complications in children with sickle cell anemia in a region with endemic malaria (Uganda, NCT01976416). These studies may expand the evidence to support the safety and efficacy of hydroxyurea in Africa and other regions with limited health care resources.

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References

1. Piel FB, Patil AP, Howes RE, Nyangiri OA, Gething PW, Dewi M, Temperley WH, Williams TN, Weatherall DJ, Hay SI. Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. The Lancet. 2013; 381(9861):142–151.
2. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet. 2014
3. McAuley CF, Webb C, Makani J, Macharia A, Uyoga S, Opi DH, Ndila C, Ngatia A, Scott JA, Marsh K, Williams TN. High mortality from Plasmodium falciparum malaria in children living with sickle cell anemia on the coast of Kenya. Blood. 2010; 116(10):1663–1668. [PubMed: 20530796]
4. Svarch E, Machin S, Nieves RM, Mancia de Reyes AG, Navarrete M, Rodriguez H. Hydroxyurea treatment in children with sickle cell anemia in Central America and the Caribbean countries. Pediatr Blood Cancer. 2006; 47(1):111–112. [PubMed: 16550531]
5. Dehury S, Purohit P, Patel S, Meher S, Kullu BK, Sahoo LK, Patel NK, Mohapatra AK, Das K, Patel DK. Low and fixed dose of hydroxyurea is effective and safe in patients with HbSbeta thalassemia with IVS1–5(G-->C) mutation. Pediatr Blood Cancer. 2014
6. Voskaridou E, Christoulas D, Bilalis A, Plata E, Varvagiannis K, Stamatopoulos G, Sinopoulou K, Balassopoulou A, Loukopoulos D, Terpos E. The effect of prolonged administration of hydroxyurea on morbidity and mortality in adult patients with sickle cell syndromes: results of a 17-year, single-center trial (LaSHS). Blood. 2010; 115(12):2354–2363. [PubMed: 19903897]
7. Kumar R, Singh K, Panigrahi I, Agarwal S. Genetic Heterogeneity of Beta Globin Mutations among Asian-Indians and Importance in Genetic Counselling and Diagnosis. Mediterr J Hematol Infect Dis. 2013; 5(1):e2013003. [PubMed: 23350016]
8. Smith-Whitley K. Reproductive issues in sickle cell disease. Blood. 2014; 124(24):3538–3543. [PubMed: 25472967]
9. Patel DK, Mashon RS, Patel S, Das BS, Purohit P, Bishwal SC. Low dose hydroxyurea is effective in reducing the incidence of painful crisis and frequency of blood transfusion in sickle cell anemia patients from eastern India. Hemoglobin. 2012; 36(5):409–420. [PubMed: 22881992]
10. Patel S, Purohit P, Mashon RS, Dehury S, Meher S, Sahoo S, Dash SS, Das K, Das P, Patel DK. The effect of hydroxyurea on compound heterozygotes for sickle cell-hemoglobin D-Punjab--a single centre experience in eastern India. Pediatr Blood Cancer. 2014; 61(8):1341–1346. [PubMed: 24616059]