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Hydroxyurea Improves Lung Function in Children with Sickle Cell Disease

ATS 2016, SAN FRANCISCO – For the first time, researchers were able to demonstrate that children diagnosed with sickle cell disease showed improvement in lung function after treatment with hydroxyurea, a treatment that is underused despite its demonstrated benefits. The study was presented at the ATS 2016 International Conference.

With 1 in 500 people affected, sickle cell disease is the most commonly inherited genetic disorder in people of African descent. "Persons with sickle cell disease experience an annual decline in lung function that starts in childhood," said Anya McLaren, MD, FRCP, MSc, lead author and respiratory medicine fellow at The Hospital for Sick Children in Toronto, Canada. "This study is the first of its kind to look at the effect of hydroxyurea on lung function. We found that hydroxyurea improves annual pulmonary function decline in children with sickle cell disease by more than one-third."

After receiving the treatment, all 94 study participants age 6 to 20 years old were followed for four years and their blood count, hemoglobin F, liver and renal functions measured at certain time points beginning at three months. Two measures of lung function – FEV1, which measures how quickly a person can move air out of his/her lungs, and FEF25-75, which helps determine if there is an obstruction in the airway – were taken before and after hydroxyurea. There was significant improvement in both FEV1 and FEF25-75 after treatment.

More than a decade of research in young people has produced data on the safety and effectiveness of hydroxyurea. Despite the evidence, Dr. McLaren believes clinicians' concerns about patient non-compliance and fears of potential side effects, namely carcinogenesis, are the primary reasons hydroxyurea is underused. But some of those fears may be unfounded.

“Long-term observational studies suggest beneficial effects without excessive damage to bone marrow, deleterious effects on growth and development, altered fertility, accumulation of mutations or increased carcinogenicity,” said Dr. McLaren.

“Evidence that lung function may be better preserved while on hydroxyurea may encourage compliance and adherence to this medication for patients with sickle cell disease,” added Dr. McLaren. “In combination with the established safety data, it hopefully will promote physician recommendations for hydroxyurea initiation and encouragement of compliance.”

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Abstract 6146
Effect of Hydroxyurea on Pulmonary Function Decline in Children with Sickle Cell Disease

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Abstract Body

Introduction
Sickle cell disease (SCD) is one of the most common inherited blood disorders, affecting 1 in 600 African Americans. Pulmonary complications are the leading cause of morbidity and mortality in adults with SCD and a low FEV1 is predictive of earlier death. Hydroxyurea (HU) is known to decrease the number of acute sickle-related events such as pain and acute chest crises (ACS). We hypothesize that hydroxyurea (HU) therapy prevents the expected annual decline in pulmonary function in children with SCD.

Methods
Research Ethics Board approval was obtained for this project. Study participants were initiated on HU as decided by the treating hematologist. Participants were followed clinically over a 4-year period at 3, 6, 9, 12, 24, 36 and 48-month time points after HU initiation in Sickle Cell Clinic. Laboratory measurements (complete blood count, hemoglobin F, liver and renal function tests) were monitored at each of these time points. Pulmonary function tests (PFT) were collected up to median of 3.68 years pre and 3.84 years post initiation of HU. Percent predicted values were calculated using the NHANES reference equations. Linear regression analysis using generalized estimating equations to account for repeated measures were used to assess how outcomes differed with the use of HU after adjusting for time and other relevant covariables.

Results

PFT measurements were analyzed in 94 children between the ages of 6 and 20 years. The average age of HU start was 11.0 (+/-4.4) years. 96% had HbSS genotype and 47% were male. There was a greater than 1-fold increase in measured hemoglobin F each year of therapy. The annual rate of decline in predicted FEV1 and FEF25-75 before HU initiation was -1.98%/year (95% CI -2.57, -1.39) and -3.59%/year (95% CI -4.43, -2.75), respectively. After HU initiation, there was a significant ($p<0.05$) improvement in the annual decline of these two parameters to -1.28%/year (95% CI -1.79, -0.76) and -2.88%/year (95% CI -3.49, -2.28), respectively. Changes in FEV1 and FEF25-75 were independent of the age at and time from HU therapy initiation. There was no significant change in TLC, FVC or FEV1/FVC predicted measurements after HU initiation.

Conclusion

Hydroxyurea therapy in children with sickle cell disease results in improvement in pulmonary function decline over time. Not only do these findings support the use of hydroxyurea in children with SCD but may provide some insight into the pathophysiology of solid organ manifestation i.e. lung disease in SCD.