Cerebral Blood Flow in Adolescents with Sickle Cell Anemia Receiving Voxelotor

Jeremie H. Estepp, MD[1]; Winfred Wang, MD[1]; Scott Hwang, MD, PhD[2]; Claudia Hillenbrand, PhD[2]; Robert Ogg, PhD[2]

Departments of [1]Hematology and [2]Diagnostic Imaging at St. Jude Children's Research Hospital, Memphis, TN, USA

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Background

- Oxygenated sickle hemoglobin (HbS) does not polymerize.
- Increasing oxygen affinity to HbS is a therapeutic strategy for sickle cell disease.
- Voxelotor (GBT440) is a first-in-class, small molecule that increases the affinity of hemoglobin for oxygen and inhibits polymerization.
- It has been postulated that increasing hemoglobin-oxygen affinity could limit oxygen offloading from hemoglobin, thus impairing tissue oxygenation which could lead to an increase in cerebral blood flow (CBF), and potentially increase the risk of stroke.
- We used MRI techniques to evaluate cerebrovascular hemodynamics to inform on cerebral oxygenation in children receiving voxelotor.

Aim

- To examine effect of voxelotor on grey matter CBF in children with SCA

Methods

- This was a St. Jude Children's Research Hospital (St. Jude) investigator-initiated, pilot and ancillary study of the ongoing HOPE-KIDS1 (NCT02850406) trial.
- Study activities were IRB approved and all participants provided informed consent.
- Participants underwent two functional magnetic resonance imaging with angiography (MRI/MRA) evaluations on a 3T MR scanner utilizing a multi-channel head coil.
  1. Baseline prior to receiving voxelotor
  2. Following at least 4 weeks of daily voxelotor
- Arterial spin labeling (ASL) was used to measure resting state CBF.

Financial Sponsor

Global Blood Therapeutics, Inc funded the cost of MRI evaluations, but did not design the study or analyze the data.

Conflict of Interest

None

Results

Table 1. Demographics and Treatment Variables

Cases	A	B	C
Genotype	HbSβ^{0}thal	HbSS	HbSS
Age, y	14.6	12.8	14.3
Sex	Male	Female	Female
Height, cm	167.7	154.8	166
Weight, kg	58.9	39.4	60.3
Hydroxyurea, mg/kg	26.2	30.2	26.5
Voxelotor, mg	900	900	1500

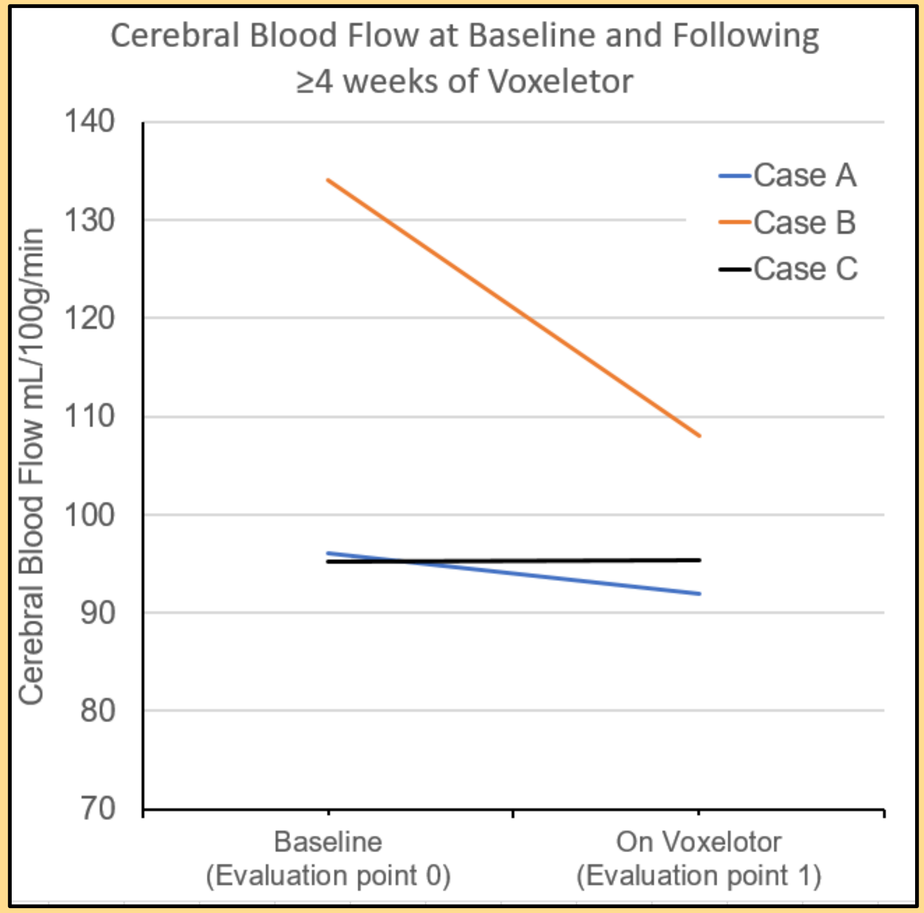
Table 2. Days on Study and Laboratory Parameters

Cases	A		B		C	
Evaluation point	0	1	0	1	0	1
Time on study, days	-4	36	-4	80	0	56
Laboratory Parameters						
Hb, g/dL	11.3	11.4	7.4	8.0	10.6	11.6
MCV, fL	79.4	78.1	94.0	83.4	134.9	132.1
HbF, %	5.5	--	4.2	--	24.4	--
EPO, mU/mL	47	44	129	135	267	196
ARC, cells x10^9/L	227	306	330	306	163	142
LDH, units/L	476	479	688	625	455	406
Bili, mg/dL	2.4	2.5	2.5	1.7	1.8	1.3

Hb, hemoglobin; MCV, mean corpuscular volume; HbF, fetal hemoglobin; EPO, erythropoietin; ARC, absolute reticulocyte count; LDH, lactate dehydrogenase; Bili, bilirubin

Key Results:

1. All participants (Table 1) were receiving hydroxyurea.
2. As per the HOPE-KIDS1 design, two participants received 900 mg/day and one received 1500 mg/day of voxelotor.
3. Baseline MRI/MRAs were normal in two cases (A&C) and case B had silent cerebral infarcts without vasculopathy.
4. Cases tended to have higher hemoglobin levels and less hemolysis while receiving voxelotor (Table 2).
5. As expected, two cases (A&B) had lower CBF after receiving voxelotor (Figure).
6. Repeat MRI/MRAs following chronic voxelotor showed no new or evolving areas of ischemia.



Summary

- **Vasodilatory autoregulation of the cerebral vasculature allows for titration of blood flow to the brain based on metabolic demand (Guilliams, K. *Stroke* 2019).**
- **In a small cohort of adolescents with SCA, the lack of increase in CBF after treatment with voxelotor suggests that there is no impairment in oxygen unloading to brain tissue.**
- **These preliminary findings of decreasing CBF with rising hemoglobin levels in two patients (Cases A&B) suggest improved oxygen delivery to the brain.**
- **Further study on the effects of voxelotor on cerebral hemodynamics and oxygen delivery is warranted.**