GBT1118 Diminishes Vaso-Occlusion in Sickle Cell Disease Mice

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O2, oxygen; pO2, partial pressure of oxygen; RBC, red blood cell.

**METHODS**

**INTRODUCTION**

Sickle cell disease (SCD) is an inherited disorder caused by a mutation in the j-chain of hemoglobin (Hb) that leads to the production of sickle Hb (Hbs). When deoxygenated, Hbs polymerizes into rigid shapes that deform red blood cells (RBCs) into a sickle shape and damage cell membranes. One of the most debilitating complications of SCD is recurrent, painful vaso-occlusive events. These involve heterogeneous cell clusters comprising sickled RBCs, neutrophils, and platelets that bind to activated endothelial cells. Recent clinical efforts to prevent vaso-occlusive events primarily target the inflammatory downstream component of the disease. GBT1118, a structural analog of voxelotor (GBT440), binds covalently and reversibly via an imine intermediate to the N-terminal valine of the Hb α-chain and increases the Hb affinity for oxygen.2

The present work studies the direct impact of GBT1118 on vaso-occlusion in a dorsal skinfold model in Niles-Txews SCD mice.1,2

**RESULTS**

Figure 2. GBT1118 Increases Hb–O2 Affinity (A) and Reduces Sickling (B) in Blood From a Patient With SCD

**Figure 3. GBT1118 Increases Hb–O2 Affinity (A) and Reduces Ex Vivo Sickling (B and C) in a Marine Model of SCD

**Figure 4. GBT1118 Reduces the Number of Sickled RBCs by Approximately 4-fold In Vivo

**Figure 5. GBT1118 Concentrations Remain Unchanged During Hypoxia/Reoxygenation Challenge

**Figure 6. Treatment With GBT1118 Increases the Number of Patent Vessels by 2-fold in SCD Mice

**Figure 7. Treatment With GBT1118 Limits Vaso-Occlusion Following Hypoxia/Reoxygenation Challenge

**SUMMARY

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In blood from a patient with SCD, GBT1118, a structural analog of voxelotor, shifted the oxygen equilibrium curve and reduced RBC sickling in a dose-dependent manner (Figure 4). Similarly, a leftward shift of the oxygen-equilibrium curve and reduced sickling were observed ex vivo in blood from SCD mice while improved survival has been described in hypoxia-challenged SCD mice treated with alamotuzumab and sickle cell modulators of Hb.5,7 The present study demonstrates for the first time that an allosteric modifier of Hb can improve vascular patency and reduce vaso-occlusion in a mouse model of SCD.

**CONCLUSION

The allosteric Hb modifier GBT1118, an analog of voxelotor, improved vascular patency in a mouse model of SCD both before and after challenge with hypoxia/reoxygenation, possibly by delaying hypoxia-triggered Hb polymerization sufficiently for RBCs to transist the microcirculation without sickling or adhering to the vessel wall. These results support the potential for hemoglobin modifiers to improve sickle, vaso-occlusion and micobvascular flow in patients with SCD, thus modifying both the acute and chronic complications of the disease.

**REFERENCES

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**DISCLOSURE

The authors declare that they have no competing interests.

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