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Voxelotor: A Hemoglobin S Polymerization Inhibitor for the Treatment of Sickle Cell Disease

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Sickle cell disease (SCD) affects millions of people throughout the world. Hemoglobin S (HbS) polymerization is the fundamental cause of SCD pathophysiology, which leads to hemolysis, increased viscosity, and acute vaso-occlusive episodes. Novel agents have been developed to target the pathophysiology of SCD and decrease the frequency of SCD complications. Voxelotor (Oxbryta) is an HbS polymerization inhibitor that is approved by the U.S. Food & Drug Administration for the treatment of SCD in adults and pediatric patients 12 years and older.

Sickle cell disease (SCD) is characterized by a single amino acid substitution in the gene that encodes for the B-globin subunit of hemoglobin. The autosomal recessive gene creates hemoglobin S (HbS), which polymerizes reversibly when deoxygenated to form a gelatinous network of fibrous polymers that firms the red blood cell (Gardner, 2018; Yawn et al., 2014). This form of hemoglobin also increases viscosity, causes dehydration, and creates the sickle shape. These abnormalities can cause hemolysis, vaso-occlusion, and inflammation, which lead to acute complications, including stroke, acute chest syndrome, and vaso-occlusive pain crises (Kato, Piel, & Reid, 2018). Long-term complications of SCD include chronic kidney disease, anemia, and hepatotoxicity, which can result in multiorgan failure and death (Blair, 2020; Kato et al., 2018).

Acute vaso-occlusive pain, a hallmark sign of sickle disease, occurs when erythrocytes adhere to the inner lining of the vasculature and result in blockage and, subsequently, acute pain episodes. Vaso-occlusive crises are the most common complication of SCD and one of the more frequent reasons for emergency room visits in this population (Brousseau, 2010; Centers for Disease Control and Prevention, 2019). Standard treatment for pain crises includes optimizing the dose of hydroxyurea and opioids to manage the pain (Eaton & Bunn, 2017; Gardner, 2018). However, approximately 30%

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of patients have persistent pain episodes despite optimal doses of hydroxyurea (Centers for Disease Control and Prevention, 2019; Gardner, 2018). Until recently, there have been no therapeutic options for these patients. One novel option is voxelotor.

Voxelotor (Oxbryta), an HbS polymerization inhibitor, was granted approval by the U.S. Food & Drug Administration (FDA) in 2019 for the treatment of SCD in adults and pediatric patients 12 years and older. Voxelotor was granted accelerated approval based on results of the phase III HOPE trial (Vichinsky et al., 2019) A post-approval confirmatory trial, HOPE-KIDS 2, is underway as a condition of approval.

MECHANISM OF ACTION

Voxelotor binds reversibly to hemoglobin, stabilizing the oxygenated hemoglobin state and preventing HbS polymerization by increasing hemoglobin's affinity for oxygen. Preclinical studies demonstrate that voxelotor increases hemoglobin's affinity for oxygen and decreases HbS polymerization in a dose-dependent manner (Howard, Hemmaway, & Tefler, 2019). Voxelotor may inhibit red blood cell sickling, improve red blood cell deformability, and reduce whole blood viscosity, which contributes to anemia and hemolysis (Global Blood Therapeutics, 2019).

CLINICAL TRIALS

Howard and colleagues (2019) evaluated the safety and tolerability of single and multiple doses of voxelotor in healthy volunteers and SCD patients as a phase I/II trial. Voxelotor was administered as multiple doses (500 mg, 700 mg, or 1,000 mg) for 28 days and multiple doses (700 mg or 900 mg) for 90 days. Patients who were in the 900 mg/day for 90 days cohort group, along with patients who were interested, were offered continuation in the open-label extension study for 6 months. The trial enrolled 38 SCD patients in the 28-day cohorts and 16 SCD patients for the 90-day cohorts. Four SCD patients received voxelotor 900 mg daily for 90 days in the extension study. At 2 weeks of treatment, all doses of voxelotor resulted in an increase in median hemoglobin levels (baseline range 7.9–8.1 g/dL and median increase of 1.0 g/dL) and a reduction in clinical laboratory markers of hemolysis. Long-term dosing with 900 mg daily showed durable improvement in median hemoglobin of at least 1 g/dL. Treatment with voxelotor was associated with dose-dependent increase in hemoglobin affinity for oxygen and is well tolerated at doses up to and including 1,000 mg daily for 28 days and 900 mg daily for 6 months (Howard et al., 2019). Overall, this study suggested that voxelotor has a favorable benefit-risk profile for patients with SCD-related anemia and can serve as a potential disease-modifying therapy in SCD.

The phase IIa HOPE-KIDS 1 trial demonstrated that the pharmacokinetics of voxelotor in adolescents between 12 to 18 years old were similar to those observed in adults. Fifteen patients were given voxelotor 1,500 mg daily for 24 weeks. The authors observed that 16.55% of patients achieved an increase in hemoglobin from baseline of > 1.0 g/dL (median baseline = 8.5 g/dL). Patients had a median reduction in indirect bilirubin, lactate dehydrogenase, and percentage of reticulocytes from baseline, which is similar to the trend seen in adults (Washington, Green, & Inati, 2018).

Based on the phase I/II and IIa trials, Vichinsky and colleagues (2019) evaluated hemoglobin response with various doses of voxelotor in the phase III HOPE trial. The trial enrolled 274 patients from 12 to 65 years old with confirmed SCD and at least one vaso-occlusive episode in the past 12 months. Patients who were stable on a hydroxyurea dose for 3 months were included in the study. This trial randomly assigned patients in a 1:1:1 manner to receive once-daily doses of voxelotor 1,500 mg, voxelotor 900 mg, and placebo.

The proportion of patients with a hemoglobin response (defined as an increase from baseline of > 1.0 g/dL) at 24 weeks was 31% in the 900-mg group (p = NR in comparison to placebo), 55% in the voxelotor 1,500 mg group ($p < 0.001$ in comparison to placebo), and 7% in the placebo group (Vichinsky et al., 2019). Higher rates of hemoglobin response were seen in the voxelotor 1,500 mg group regardless of hydroxyurea use. Additionally, voxelotor 1,500 mg daily was associated with significant reduction in indirect bilirubin (–29.1% vs. –3.2%) and percentage of reticulocytes (–4.5% vs. 3.4%) compared with placebo ($p < .001$, Table 1). Annualized incidence rate of vaso-occlusive crises was 2.76 crises per person-year in the voxelotor 900 mg group, 2.77 in the voxelotor 1,500 mg

Table 1. Change in Hemoglobin Levels and Markers of Hemolysis from Baseline to Week 24

	Voxelotor 1,500 mg		Voxelotor 900 mg		Placebo	
	Number of participants	Change from baseline to week 24 (95% CI)	Number of participants	Change from baseline to week 24 (95% CI)	Number of participants	Change from baseline to week 24 (95% CI)
Absolute change in hemoglobin, g/dL	88	1.1 (0.9 to 1.4)	92	0.6 (0.3 to 0.8)	91	−0.1 (−0.3 to −0.2)
Relative change in indirect bilirubin level, %	85	−29.1 (−35.9 to −22.2)	88	−20.3 (−27.1 to −13.6)	85	−3.2 (−10.1 to 3.8)
Relative change in percentage of reticulocyte, %	88	−4.5 (−11.9 to 2.8)	92	−1.3 (−10.3 to 7.7)	91	3.4 (−4.0 to 10.9)

Note. All statistical analyses performed were a least-squares regression model. Absolute change in hemoglobin, relative change in indirect bilirubin level, and relative change in percentage of reticulocytes were considered statistically significant for the voxelotor 1,500 mg group in comparison to the placebo group ($p < .001$). Information from Vichinsky et al. (2019).

group, and 3.19 in the placebo group (p = NR; Vichinsky et al., 2019).

ADVERSE EFFECTS

In the HOPE study, treatment-related adverse effects were observed in 32%, 39%, and 25% of patients in the voxelotor 900 mg daily, voxelotor 1500 mg daily, and placebo groups, respectively (Vichinsky et al., 2019). Corresponding rates of serious adverse events were 3%, 3%, and 1%, respectively. The most common adverse effects that occurred in ≥ 5% of patients were diarrhea, headache, nausea, abdominal pain, and rash with a higher incidence in the voxelotor 900 mg and the voxelotor 1,500 mg group (Table 2).

DOSING AND ADMINISTRATION

The recommended starting dose of voxelotor is 1,500 mg once daily with or without hydroxyurea (Global Blood Therapeutics, 2019). Voxelotor can be administered with or without food. If a dose is missed, it is recommended to continue dosing the next day. The tablets should be swallowed whole and should not be crushed, cut, or chewed (Global Blood Therapeutics, 2019).

Voxelotor is a major CYP3A4 substrate. If a strong CYP3A4 inhibitor or inducer is utilized, the prescribing information recommends to change the dose of voxelotor. For strong CYP3A4 inhibitors or in severe liver impairment (defined as Child-Pugh Class C), the dose of voxelotor should

Table 2. Treatment-Related Adverse Events

Adverse event	Voxelotor 1,500 mg (N = 88)	Voxelotor 900 mg (N = 92)	Placebo (N = 91)
Diarrhea	11 (12.5%)	8 (8.7%)	3 (3.3%)
Nausea	6 (6.8%)	6 (6.5%)	5 (5.5%)
Abdominal pain	6 (6.8%)	6 (6.5%)	1 (1.1%)
Rash	7 (8.0%)	2 (2.2%)	4 (4.4%)
Headache	5 (5.7%)	3 (3.3%)	3 (3.3%)
Abdominal pain upper	2 (2.3%)	2 (2.2%)	2 (2.2%)
Vomiting	1 (1.1%)	3 (3.3%)	4 (4.4%)
Dermatitis acneform	1 (1.1%)	1 (1.1%)	0
Hypoesthesia	1 (1.1%)	0	1 (1.1%)
Migraine	1 (1.1%)	0	1 (1.1%)
Fatigue	0	2 (2.2%)	0
Pyrexia	0	2 (2.2%)	0
AST increased	0	2 (2.2%)	0
Decreased appetite	0	2 (2.2%)	0
Paresthesia	0	1 (1.1%)	1 (1.1%)
Pruritus	0	1 (1.1%)	1 (1.1%)
Dizziness	0	0	3 (3.3%)

Note. Adverse events between each of the groups did not differ significantly. The most common side effects were diarrhea, nausea, and abdominal pain.
AST = aspartate aminotransferase. Information from Vichinsky et al. (2019).

be reduced to 1,000 mg once daily (Global Blood Therapeutics, 2019). According to the package insert, there are no dose adjustments for patients with renal dysfunction and no clinical significant effect on the excretion of voxelotor (Global Blood Therapeutics, 2019). For moderate to strong CYP3A4 inducers, the recommended dose of voxelotor is 2,500 mg once daily (Global Blood Therapeutics, 2019).

IMPLICATIONS FOR THE ADVANCED PRACTITIONER

Voxelotor has a novel mechanism of action that has the potential to be a disease-modifying agent for patients with SCD. Although this treatment option has not been compared with other agents, such as L-glutamine and crizanlizumab, voxelotor can reduce vaso-occlusive episodes in patients who tolerate hydroxyurea. Patients who received voxelotor in the HOPE trial showed significant improvement in hemoglobin, indirect bilirubin, and percentage of reticulocytes, all of which signify improved red cell deformity and reduced blood viscosity (Vichinsky et al., 2019).

Practitioners should be aware of the drug interactions associated with the use of this drug. Because voxelotor undergoes phase I oxidation via the CYP3A4 pathway, strong CYP3A4 inducers (e.g., rifampin) and CYP3A4 inhibitors (e.g., fluconazole) can impact the serum concentration of voxelotor (Global Blood Therapeutics, 2019). Therefore, it is imperative to evaluate current drug therapies before initiating patients on voxelotor. Furthermore, the dose of voxelotor may need to be reduced in severe liver impairment, so monitoring liver function at initiation and throughout treatment may be necessary.

Voxelotor is one of three new agents to enter the market for the treatment of SCD and can potentially add benefits to the current treatment algorithm. Crizanlizumab (Adakveo), which was FDA approved in November 2019, was shown to lower the rate of sickle cell–related pain crises (1.63 vs. 2.98 crises per year, $p = .01$) and prolonged the time to first (4.07 vs. 1.38 months, $p < .001$) and second crises (10.32 vs. 5.09 months, $p < .001$) when compared with placebo, which is an area that voxelotor has not demonstrated efficacy in as of yet (Ataga et al., 2017). Additionally, L-glutamine, which was approved in 2017, demonstrated reductions in acute pain crises (3 vs. 4 crises, $p = .005$) and fewer hospitalizations (2 visits vs. 3 visits, $p = .005$) compared with placebo, which is similar to voxelotor (Niihara et al., 2018). Comparing all three of these agents, voxelotor can provide improvement in hemoglobin levels and signs of hemolysis, which is a novelty. More studies would need to be conducted, possibly comparing the agents together, to accurately place voxelotor in the sickle treatment algorithm.

An open-label extension of the HOPE trial is currently underway to assess the safety, frequency of SCD complications, and indications of hemolysis in patients (Washington Goldstein, & Dixon, 2018). About 176 patients from the phase III HOPE trial are enrolled so far, and it is expected to be complete by December 2024. Additionally, there is a pediatric open-label trial that is currently enrolling patients by invitation that is evaluating long-term safety and frequency of SCD complications in patients who have already participated in the HOPE-KIDS trial (Brown et al., 2018). Beyond just examining the long-term effects of voxelotor, there is a phase II study that is evaluating voxelotor doses between 1,500 mg to 3,000 mg to target a maximum effective dose. Once the results of these ongoing trials are published, practitioners will have a better idea of the safety, efficacy, and tolerability of voxelotor on a long-term basis.

CONCLUSION

Voxelotor is a novel HbS polymerization inhibitor indicated for the treatment of SCD in adults and pediatric patients 12 years and older. In current studies, voxelotor shows an increase in hemoglobin and decrease in laboratory markers indicative of hemolysis. Studies comparing the long-term efficacy and safety of voxelotor are needed to fully understand its place in therapy.

Disclosure

The authors have no conflicts of interest to disclose.

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