Voxelotor: A Drug Shedding Light on Sickle Cell Disease Patients

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Abstract: Sickle cell disease has been affecting millions of people all around the world, but it was never the focus in pharmaceutical researches until recent years. A novel 2019 FDA-approved drug, voxelotor, was developed as a silver lining for the millions who suffer from sickle cell disease. Voxelotor reversibly binds to hemoglobin to prevent red blood cells from sickling and destruction. Phase 1/2 and phase 3 clinical trials both revealed increased hemoglobin levels and reduced sickles cells in sickle cell disease patients. Voxelotor forms covalent bonds with the N-terminal α chain of Hb to increase its oxygen affinity, which improved patient clinical performance. Single doses of voxelotor are well tolerated in both healthy volunteers and SCD patients, but multiple doses in healthy subjects revealed more severe side effects, such as jaundice and leg ulcers. Although common adverse effects have been identified, more researches about side effects need to be studied. This review will first introduce the background of the disease and voxelotor, including basic drug properties. Followed by the efficacy of voxelotor and adverse reactions as well as risks associated with it.

1. Introduction

The underlying mechanism of sickle cell disease (SCD) is to change the shape of normal red blood cells (RBCs) which will lead to painful symptoms including pain in the joints, low oxygen in the body, malaise, etc. In the US, the majority of the victims of SCD have ancestors from Africa. Due to financial and psychosocial reasons, SCD was never the focus of pharmaceutical researches until recent years, some drugs can assuage the symptoms, however, a recently discovered drug, voxelotor, is proved to be able to change the hematological parameters in a way that can save SCD patients' lives.

Voxelotor targets hemoglobin (Hb) in RBCs to terminate polymerization of Hb and consequently prevent RBCs sickling. The pharmacokinetic profile is well established following vast clinical trials. Efficacy and adverse effects of voxelotor were identified in both phase 1/2 and phase 3 clinical trials, as well as in individual case reports.

2. Sickle Cell Disease and voxelotor

2.1 Overview of Sickle Cell Disease

SCD is a severe and life-threatening inherited chronic disorder causing RBCs to misshape and to contort into a sickle shape due to a single mutation of the β chain of hemoglobin (Hb), a protein carried by red blood cells that carries oxygen to tissues and organs throughout the body. In the mutated sickle hemoglobin (HbS), a hydrophilic βGlu6 is exchanged to a hydrophobic βVal6, which is from one Hb tetramer and a hydrophobic cavity from a laterally located Hb tetramer, resulting in the polymerization of deoxygenated HbS and subsequent sickling of RBCs when the oxygen level is low [1, 2]. The solubility of HbS decreases drastically especially in the capillary area with low oxygen partial pressure, leading HbS to form a semi-gel state, which gathers into a tubular shape and bends RBCs into a sickle

shape, a condition known as falcate degeneration. Sickle cell is reversible at first but becomes permanent with recurrent hypoxia.

The sickle cells break apart easily and die early, which causes a shortage of healthy RBCs, and when they travel through blood vessels, they clog the blood flow, which is very likely to cause vasoocclusive crisis (VOC), splenic sequestration crisis (SSC), acute chest syndrome (ACS), and other problems increasing the risk of untimely demise [3,4]. These problems typically start in babies of five months [5]. SCD has significant morbidity and reduces life expectancy dramatically by 30 years on average and has a devastating impact on approximately 100,000 people in the United States alone and millions more worldwide [1].

There are different genres of SCD, sickle cell anemia, sickle hemoglobin-C disease, sickle beta-plus thalassemia, and sickle beta-zero thalassemia are of more chances to occur compared to other types [6]. The median age at death for patients with sickle cell anemia (homozygous for HbS) is 42 years for males and 48 years for females. The median age at death for patients with sickle cell hemoglobin-C disease is 60 years for males and 68 years for females [7].

People who carry sickle cell trait (SCT) are with one sickle cell gene. This does not usually cause very severe problems. In America, SCD occurs among about 1 out of every 365 Black or African-American births, while for Hispanic-American births, it drops to about 1 out of every 16,300. The vast majority of the people who suffer from SCD seem to be African Americans, and about 1 in 13 Black or African-American babies is born with SCT [8]. Thus, they are at a much higher risk of getting SCD, because the sickle trait can be passed on to the next generation. If one parent carries SCT and the other parent has the normal type of Hb, the chance of the baby being born with SCT with each pregnancy is 50%. If both of the parents carry SCT, the chance of the child having SCD and the chance of the child not carrying SCT at all are both 25%.

More than one billion dollars has been spent on the treatment targeting the acute and chronic damage caused by SCD alone every year in the past century since the existence of SCD in the medical consciousness, which is one of the reasons that it was not a pharmaceutical research focus until recent years. Other than financial issues to the healthcare system, the unpredictable sequelae that have the potential to contribute to others make it almost impossible to cure the disease, which led to frustration in the discovery of drugs targeting SCD. To date, no approved drug can cure SCD via targeting the underlying disease mechanism. Hydroxyurea and L-glutamine are the only approved drug therapy [9]. Hydroxyurea, a cytotoxic drug, has safety issues involved including myelosuppression, teratogenicity, and expression of fetal Hb [10]. However, the treatment is ineffective for patients with Hb SS type SCD and sickle beta zero thalassemias, as well as selected patients with other genotypes depending on clinical course, despite the fact that it alleviates the frequency of painful episodes and ACS, which improves survival [11, 12]. L-glutamine prevents the period of VOS partially, but it does not improve any hematological parameters [12]. It is used in adult and pediatric patients 5 years of age and older to mitigate the acute complications from SCD [14]. Crizanlizumab has also been proved to be effective in reducing the number of vasoocclusive pain or ACS episodes. Hematopoietic stem cell transplantation can be effective for a few patients. However, there is still a need to reduce hemolysis that leads to an increase in Hb levels.

2.2 Overview of Voxelotor

It has been proved that the oxygenation of Hb inhibits the polymerization of Hb, as a result, the pathology of SCD can be modified by increasing the oxygenation of Hb [9]. 5-hydroxymethylfurfural (5HMF), valerosol (BW12C), and other Hb allosteric modifiers have previously been found to bind in a 2:1 stoichiometry. 5-HMF has poor pharmaceutical properties, which has resulted in few additional investigations. BW12C reduces sickling of RBCs (in vitro) and the incidence of hemolysis, which inhibits Hb polymerization without limiting oxygen delivery to the tissues and organs, by increasing the affinity between Hb and oxygen by 20%-30%. A new potent allosteric effector of sickle cell Hb, GBT440, was discovered. Compared to other allosteric modifiers, it not only increases the oxygen affinity of Hb both in vivo and vitro, but it increases the delay time to the onset of polymerization as well [2]. X-ray analysis reveals that GBT440 binds to a single α chain in a 1:1 stoichiometry to the Hb

tetramer. In rats, dogs, and monkeys, GBT440 preforms favorable pharmacokinetics, and the oral bioavailability is 60% in rats [2].

Global Blood Therapeutics has developed an HbS polymerization inhibitor voxelotor, under the brand name Oxbryta, for use in patients with SCD based on the previous studies of GBT440, it is the first of its kind oral medication and a breakthrough therapy for SCD, which makes it the reason why it is chosen for this report. It is approved by The US Food and Drug Administration (FDA) on November 25, 2019, and is given the status of the orphan drug in rare pediatric diseases [15]. The potential theoretical risks of taking the drug include tissue hypoxia that could lead to end-organ dysfunction, which is caused by the ineffective tissue oxygen extraction with the high Hg occupancy from voxelotor-bound Hg. However, such clinical cases have not been identified to date. Overall, the safety profile of voxelotor appears to be acceptable for the proposed dose so far. The long-term safety of the drug will be monitored and assessed with post-marketing requirements and commitments [14].

The molecular formula of voxelotor is $C_{19}H_{19}N_3O_3$, and its molecular weight is 337. Voxelotor is a reversible HbS polymerization inhibitor that binds to the N-terminal α chain of Hb covalently and modulates Hb affinity for oxygen. Voxelotor binding stabilizes RBCs in an oxygenated state, which blocks Hb polymerization and consequently prevents the sickling and destruction of RBCs. Studies have suggested that decreased RBC sickling would lead to reduced RBC malformation and extended RBC half-life, which results in decreased viscosity of whole blood, hemolysis, and subsequent anemia [16].

3. Pharmacology of voxelotor

3.1 Pharmacodynamics

Hb affinity for oxygen is increased by voxelotor administration and indicates a dose-dependent pattern, which is demonstrated by the linear correlation between voxelotor exposure and change in p20 and p50 (partial pressure of oxygen at which Hb oxygen saturation of 20%/50% is achieved). Hemolysis, indicated by dense RBCs, unconjugated bilirubin, and percentage of sickled red cells, is reduced dose-dependently following voxelotor treatment and the effects maintained more than 90 days [17].

3.2 Pharmacokinetics

Voxelotor is predominantly distributed into RBCs when absorbed into the blood because it prefers to bind to Hb (99.8% bound in vitro). Accumulation of voxelotor was hypothesized according to single-dose data in SCD patients and is consistent with voxelotor exposure. Following metabolization, voxelotor is mainly eliminated by the excretion of metabolites into urine and feces. [17].

Voxelotor demonstrates a linear pharmacokinetic profile. Following oral administration, the median plasma and whole blood Tmax of voxelotor are reached in 2 hours. Vary from 6 to 18 hours following oral administration, mean peak concentration is reached in whole blood and RBCs. Continuous administration of voxelotor for 8 days could achieve steady-state concentrations. A high-fat, high-calorie meal increased the voxelotor area under the curve (AUC) by 42% and Cmax by 45% in whole blood compared to the fasted state, and increased AUC by 42% and Cmax by 95% in plasma [17].

The volume of distribution of voxelotor of the central compartment is 338 L and 72.2 L in the peripheral compartment. The blood-to-plasma ratio is about 15:1 in SCD patients. The metabolization of voxelotor is extensive via Phase I (oxidation and reduction), Phase II (glucuronidation), and combinations of Phase I and II hepatic metabolizations, reported by in vitro and in vivo studies. CYP3A4 plays a major role in the oxidation of voxelotor, while CYP2C19, CYP2B6, and CYP2C9 also contribute minorly. The terminal half-life and the estimated apparent clearance of Voxelotor are approximately 35.5 hours and 6.7 L/h, respectively. Its metabolites are excreted into feces (33% as unchanged drug) and in the urine (0.1% as unchanged drug) [17].

4. Voxelotor in treatment of SCD

4.1 Clinical Efficacy

Howard et al conducted a double-blind, randomized, placebo-controlled study. Participants were divided into two groups, one with voxelotor administration for 28 days, the other was treated with voxelotor for 90 days. The 28-day group was then separated into three groups, in which voxelotor dosage was 500, 700, and 1000 mg. On the other hand, a 700 mg and a 900 mg group were created in the 90-day group. Each group consisted of eight patients, six of whom took voxelotor and two of whom took the placebo, but 16 patients of the two groups took 500 mg and 700 mg over a 28-day period. Four patients in the 900 mg group received up to six months of extended study. Two weeks later, all subjects who were on voxelotor revealed better laboratory parameters. They had increased Hb level and reduced hemolysis, which is a marker for SCD. These improvements were seen in all four patients who received extension study, therefore suggesting the effects of voxelotor were long-lasting. Furthermore, all patients treated with voxelotor had a reduction in sickled red cells. Sickled red cells in the 700 mg cohort were reduced by 73%, while the 900 mg cohort was reduced by 79% [18]. These data illustrate that voxelotor is a clinically valuable agent that holds promise for treating SCD and improving clinical performance in patients.

In a randomized, double-blind, placebo-controlled, multicenter trial run by Vichinsky et al, two groups were divided and consisted of 274 patients in total. Three groups were created, in which the first group contained 90 patients who were orally administered with Oxbryta 1,500 mg, the second group had 92 patients and the Oxbryta dosage was 900 mg, the rest 92 patients were assigned to the placebo group [17].

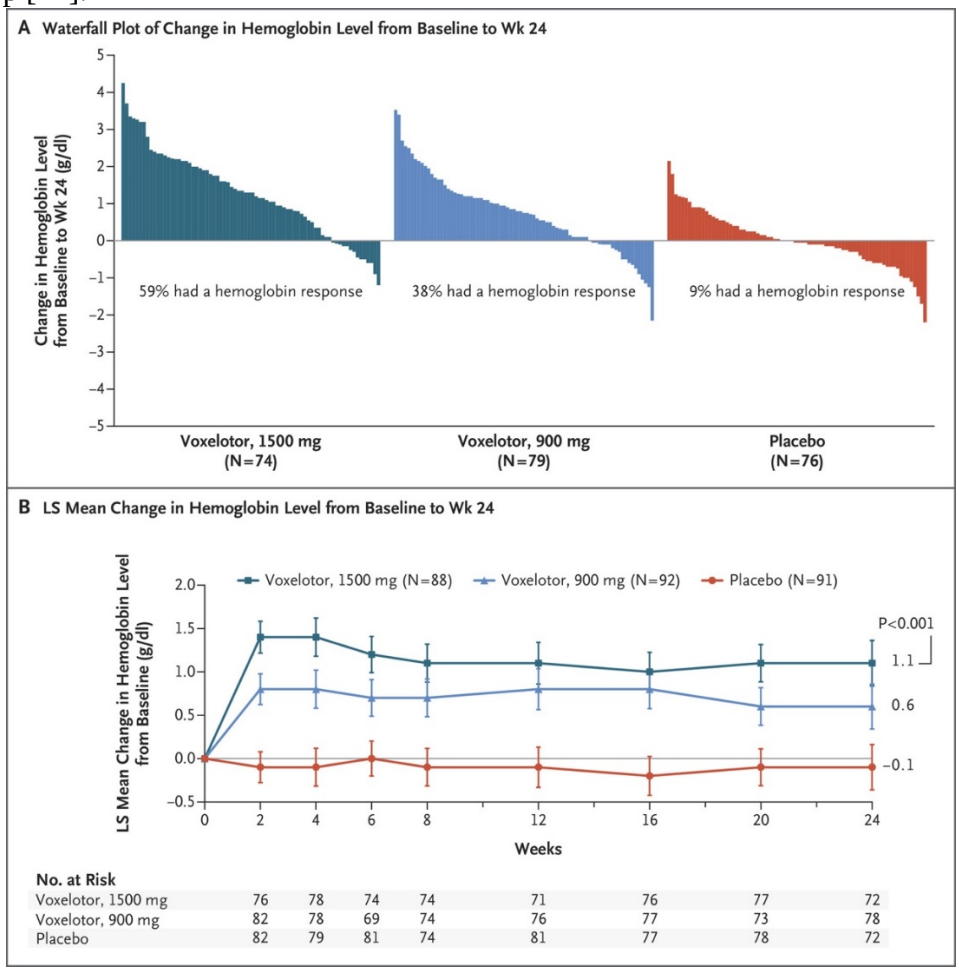

Figure 1. Change in Hemoglobin Level from Baseline to Week 24 [19].

Figure 1A demonstrated that, in the 1500-mg and 900-mg voxelotor receiving group, 59% and 38% of patients, respectively, exhibited a Hb response after 24 weeks. In contrast, only 9% of patients in

the placebo group showed a similar response. Specifically, as shown in Figure 1B, the mean Hb level in the placebo group at week 24 decreased from baseline to -0.1 grams per deciliter. In contrast, Hb level increased 1.1 g per deciliter averagely from baseline in the 1500-mg voxelotor group after 24 weeks of administration. In the 900-mg voxelotor group, the mean Hb level change was 0.6 g per deciliter.

In addition, there were fewer episodes of acute anemia in the voxelotor group compared to the placebo group. With regard to VOC, a clinical symptom that has an increased incidence in patients with SCD was less common in patients taking voxelotor. There were 183 and 179 crises in the voxelotor 900-mg and 1500-mg groups, respectively, compared to 219 crises in the placebo group [19]. These provide strong evidence that voxelotor has significant upregulation effects on the treatment of SCD.

Seven patients aged 22-67 years were treated with 900 mg of voxelotor once a day for 6 to 17 months. Two non-treatment-related death occurred. Except for this, all patients had an increase in Hb levels with voxelotor intake. Most patients increase 1 g/dL averagely, and one patient increased 5.4 g/dL after increasing the dose of voxelotor to 1500 mg. In some patients, improvements in oxygen saturation and reductions in blood transfusions were observed. During the treatment period, all patients experienced a reduction in pain caused by VOC and improvement in life quality [21].

Jaundice is a clinical manifestation of the SCD from which the patient suffers. In a phase 1/2 study, a 27-year-old male patient participated and received 900 mg voxelotor once a day for 6 months. During the study period, the patient's unconjugated bilirubin, a marker of jaundice, decreased by 76%. This patient's sense of well-being and subjective experience are revealed in the same pattern. During the treatment period, the patient felt better and had an improved quality of life, but as soon as he stopped taking voxelotor, the symptoms of jaundice recurred [22]. This case suggests that voxelotor may not only improve the test results of SCD patients but may also improve their health status.

Leg ulcers are one of the complications of SCD and can cause severe pain. In the Phase III Hemoglobin Oxygen Affinity Modulation to Inhibit HbS PolymErization Trail (HOPE) study, 22 of 274 patients had leg ulcers. Five patients received 1500 mg of voxelotor, nine patients received 900 mg of voxelotor, and eight patients received placebo. After 17 weeks, all patients in the 1500 mg voxelotor receiving group, 89% in the 900 mg group had improved or disappeared leg ulcers [23]. These data showed that voxelotor has positive effects on multiple aspects in patients with SCD.

Voxelotor is the first pharmacotherapy for SCD capable of targeting the fundamental pathogenesis of SCD. Hydroxyurea can only produce effects in a limited number of patients with SCD and safety concerns are growing, while L-glutamine can only result in decreased VOC frequency. Two other drugs that have been developed are 5-HMF and tucaresol. However, they are no longer studied due to weak pharmaceutical properties and strong immunogenicity respectively [15].

4.2 Safety and Tolerability

Safety and tolerability were tested in a phase 1/2, two-center, randomized, double-blind, placebo-controlled, three-part study (GBT440) of voxelotor in healthy volunteers and SCD patients. Multiple measures, including physical examinations, electrocardiograms, vital signs, clinical laboratory assessments, the incidence of clinical adverse events, and concomitant medications were adopted as [24].

Results indicated that voxelotor was well tolerated up to 2800 mg (highest dose tested) following single doses in healthy volunteers (n=40). Five treatment-emergent adverse events (TEAEs; diarrhea, upper respiratory tract infection, arthralgia, headache, and rash) were observed, among which related to voxelotor were diarrhea (occurred only at 2800 mg) and headache, which were only observed in >1 healthy volunteer. Four TEAEs (diarrhea, nausea, vomiting, and pain) were reported in >1 SCD patient (n=6) treated with a single dose of 1000 mg voxelotor. Excluding pain, the other three TEAEs were considered related to voxelotor. Following single-dose, all reported adverse events of voxelotor in both SCD patients and healthy volunteers were mild and classified as grade 1[23].

Following multiple doses (only evaluated in healthy volunteers; n=24), voxelotor was tolerated up to and including 900 mg daily for 15 days (highest dose tested). Three TEAEs (abdominal pain,

diarrhea, and headache) were reported in ≥10% of subjects and were considered related to voxelotor. Grade 2 (moderate) events were observed in three subjects while other adverse events were in grade 1. Headache was treated with paracetamol, while other events resolved without treatment [23].

4.3 Adverse Effects

The safety of voxelotor was tested based on data from the 179 patients in the HOPE study. In this study, 88 patients received 1500 mg of voxelotor and 99 patients received placebo. 3% of patients who received voxelotor experienced serious side effects, including headache, drug hypersensitivity, and pulmonary embolism. Rash, urticaria, mild shortness of breath, mild facial swelling, and eosinophilia are the symptoms of drug hypersensitivity. As a result of side effects, 5% of patients treated with voxelotor discontinued the drug permanently. 41% of patients treated with voxelotor changed their dose because of adverse effects. Symptoms mainly included diarrhea, headache, and skin rash (Table 1) [17].

In 2021, a 53-year-old female patient developed the first voxelotor-induced eosinophilia and systemic symptoms (DRESS) drug eruption. This patient developed acute kidney injury (AKI) and eosinophils one month after starting treatment for Hyperplasia. After stopping taking 2 weeks, the treatment was restarted. However, after 5 weeks, the patient was admitted to the hospital for various adverse reactions such as fever, fatigue, multiple skin rashes, coughing, facial swelling, AKI recurrence, and eosinophilia. Based on the diagnosis of multiple examinations, this condition is defined as an attenuating drug reaction of DRESS caused by voxelotor [24].

Table.1. Adverse Reactions (≥10%) in Patients Receiving Oxbryta with a Difference between Arms of >3% Compared to Placebo in HOPE [17].

Adverse Reaction	Oxbryta 1,500 mg (N=88)	Placebo (N=91)
Headache	23 (26%)	20 (22%)
Diarrhea	18 (20%)	9 (10%)
Abdominal Pain	17 (19%)	12 (13%)
Nausea	15 (17%)	9 (10%)
Fatigue	12 (14%)	9 (10%)
Rash	12 (14%)	9 (10%)
Pyrexia	11 (12%)	6 (7%)

4.4 Drug-Drug Interactions and Contradictions

Voxelotor is contradicting in patients who had a history of serious hypersensitivity reactions to the excipients of Oxbryta. Either strong CYP3A4 inhibitors or fluconazole should not be administered to patients taking voxelotor because of the risk of increased plasma concentrations of voxelotor. Voxelotor is also contradicted with the administration of strong CYP3A4 inducers. This is to prevent a possible decrease in plasma concentrations of voxelotor. In laboratory tests, voxelotor has shown that it can interfere with measurements of the Hb subtype [17]. It is thought that this phenomenon is due to the formation of voxelotor-Hb complexes [16]. Therefore, physicians are advised to perform chromatographic analyses when patients are not using voxelotor [17].

4.5 Special Cautions

Although administration to pregnant rats and rabbits has not been shown to have any adverse effects on the fetus, caution should be given to pregnant women as the effects on the human fetus are unknown. Voxelotor is found in rat and rabbit milk and therefore, is not recommended for lactating women, due to the risk of voxelotor being transferred to breast milk. For pediatric use, safety and efficacy studies were performed in pediatric patients aged 12 to 17 years in the HOPE trial. On the other hand, the safety and efficacy of the elderly have not been established due to the shortage of subjects. In addition, voxelotor is more exposed in patients with impaired liver function and should be given at lower doses when given to these patients. [17].

4.6 Drawbacks

Reduction of tissue oxygen delivery capacity is a theoretical deficiency of Hb-oxygen affinity modulators. This may result in a compensatory increase in erythropoietin (EPO), followed by subsequent reticulocytosis, increased red blood cell mass, and increased cardiac output under conditions of exercise stress. Several specific assessments were performed including evaluation of reticulocyte counts, EPO levels, and hemodynamic response to submaximal exercise testing to evaluate this potential problem of the drug. Healthy volunteers were administrated with up to 900 mg voxelotor daily and achieved approximately 40% Hb modification. Testing results indicated that there was no treatment-related increase in reticulocyte count or Hb level. Furthermore, EPO levels did not exceed the normal range, and no increase in resting or peak heart rate during exercise was observed [23]. However, more experimental data is still required to verify the current study since hypoxia in a certain part of the body, such as brain stroke induced by brain hypoxia can be detrimental [25].

Another problem is the risk of complications from abrupt stopping. This is due to the sudden and dramatic increase in the pathobiology of sickle cells and hematocrit. [26].

SCD is a rare disease. Establish of rare and very rare adverse effects of voxelotor administration is hard to achieve due to the lack of subjects and clinical trials. Despite the publication of several reports, there are still major loopholes in this aspect [24]. Therefore, caution should be given when using voxelotor and it is advisable to provide feedback on side effects.

4.7 Dosage and Administration

Voxelotor is available as a 500-mg oral tablet and the recommended dosage of Oxbryta (voxelotor) for pediatric patients aged ≥12 years and adults is 1,500 mg taken orally once daily with or without food for SCD [17]. For patients taking strong CYP3A4 inhibitors or fluconazole, a 500mg reduction in daily dose should be applied. For patients administering strong or moderate CYP3A4 inducers, the daily dose should be increased to 2500mg [16].

In patients with severe hepatic impairment, the daily dose is recommended to reduce to 100mg. Patients with alanine aminotransferase or alkaline phosphatase >3 times the upper limit of normal (ULN) or aspartate aminotransferase >4 times ULN were excluded from clinical trials. Patients with renal insufficiency do not require dosage adjustment. However, in the HOPE trial, patients with an estimated glomerular filtration rate <30 mL/min/1.73 m2 or on chronic dialysis were not included [16].

5. Conclusion

SCD is caused by polymerization of deoxygenated HbS, and voxelotor is an approved HbS polymerization inhibitor, which makes it a viable drug therapy for SCD. Voxelotor forms covalent bonds with the N-terminal α chain of Hb to increase its oxygen affinity, which consequently blocks HbS polymerization and achieves an increase of Hb level. The combination of inclined Hb level and reduced incidence of complications results in improved patient clinical performance. Single doses of voxelotor are well tolerated in both healthy volunteers and SCD patients, but multiple doses in healthy subjects revealed more severe side effects. Voxelotor pharmacokinetics and pharmacodynamics have been established to ensure more reliable drug delivery. As the first drug of its kind, Voxelotor has demonstrated very high clinical value in the treatment of SCE in both preclinical and clinical studies. Laboratory data used in clinical practice, Hb value, etc., have been significantly improved. SCD-related complications such as jaundice and leg ulcers will also be greatly reduced. Although common adverse effects have been identified, reports of rare and very rare side effects are still inadequate. Despite its clinical efficacy, voxelotor is suspected to cause tissue hypoxia. Voxelotor appears to be a promising treatment for SCD, more researches into how it affects AOC, ACS, and other issues including the pain are expected. Further clinical trials comparing voxelotor and other drugs that cure the same disease need to be warranted.

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