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New Drug Update

Voxelotor: novel drug for sickle cell disease

Jasjit Singh[1], Sachin Maggo[2]*, Uthara K. Sadananden[2]

[1]Department of Hematology, Government Hospital, Chandigarh, Punjab, India
[2]Department of Medicine, Government Hospital, Joshimath, Uttarakhand, India

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***Correspondence:**
Dr. Sachin Maggo,
Email: sachinmaggo2003@gmail.com

ABSTRACT

Sickle cell disease (SCD), is an autosomal recessive disorder caused by mutation in the β-chain of haemoglobin (Hb) that leads to production of sickle haemoglobin (HbS). The disease has a profound negative impact on health-related quality of life with increased propensity for complications. Current treatment options include drugs like hydroxyurea and L-glutamine that are currently on the market. However, none of these therapies target the underlying mechanism and have potential safety concerns. As oxygenated Hb is a potent inhibitor of HbS polymerization, increasing the proportion of oxygenated HbS may provide a disease-modifying approach to SCD. Voxelotor is a novel therapy developed for the treatment of SCD by modulating the Hb affinity for oxygen. By forming a reversible covalent bond with the N-terminal valine of the α-chain of Hb, the drug results in an allosteric modification of Hb and thereby leading to an increase in oxygen affinity. Moreover, voxelotor prevents sickling of red blood cells (RBCs) and possibly interrupts the molecular pathogenesis of the disease. The drug is available in oral formulation with a recommended dosage of 1500 mg once daily. The onset of voxelotor is fast, shows rapid absorption and linear pharmacokinetics. Most common adverse reactions seen are headache, diarrhea and abdominal pain. Clinical trials for voxelotor have been positive, and results suggest that the drug may be a new safe and effective option for SCD treatment. With global blood therapeutics having already received US FDA approval in November 2019, voxelotor may soon be an addition to the mounting armoury of drugs against SCD.

Keywords: Voxelotor, Sickle cell disease, Polymerization inhibitors, Anemia, Foetal hemoglobin

INTRODUCTION

Sickle cell disease (SCD), one of the most common inherited diseases worldwide, is an autosomal recessive disorder caused by a mutation in the β-chain of haemoglobin (Hb) that leads to production of sickle haemoglobin (HbS).[1] When deoxygenated, HbS polymerizes and deforms red blood cells (RBCs) into a sickle shape, leading to permanent cell membrane damage, painful vasoocclusive crisis, end-organ damage and dysfunction, and early death.[2,3] The disease is now understood to be a disorder of global importance and economic as well as clinical significance. It affects 80,000-100,000 individuals in the United States and millions worldwide.[4,5] Those affected by the disease live in areas of sub-Saharan Africa, the Middle East, India, the Caribbean, South and Central America, some countries along the Mediterranean Sea, as well as in the United States and Europe.[6]

Numerous modalities for the treatment of sickle cell disease have been encompassed in the past three decades including the introduction of penicillin prophylaxis for children with sickle cell, the institution of newborn screening programs, and the use of transcranial Doppler screening for detection of cerebral vasculopathy and

stroke prevention.[7-9] However, there is unmet need for better treatments of sickle cell. Ideally, a treatment approach is needed that does not just address pain or treat and prevent sequelae of the disease (e.g., susceptibility to infection from asplenia). Rather, a treatment approach that targets the pathophysiology of the disease would be more prudent. Currently the only available approved disease-modifying medications for SCD are hydroxyurea and L-glutamine. Hydroxyurea is not effective in some patients and has significant safety concerns, including potential embryofetal toxicity and myelosuppression.[10] L-glutamine, recently approved, demonstrated only a modest effect in prevention of vaso-occlusive crisis without improvement in haematologic parameters, and does not target the pathophysiologic mechanism of disease.[11,12] Therefore, a chronic preventive treatment remains a serious unmet need.

Haemoglobin oxygen affinity modulation to inhibit HbS polymerization is a promising and potentially disease modifying strategy for treating SCD.[13-15] Previous Hb allosteric modifiers such as 5-hydroxymethylfurfural (5-HMF), tucaresol, and valerosol (BW12C) have been investigated.[16-19] These agents (tucaresol and valerosol) demonstrated that increasing the Hb-oxygen affinity at 20–30% Hb modification inhibited RBC sickling in vitro and reduced haemolysis in SCD patients without compromising oxygen delivery to tissues. However, poor pharmaceutical properties (5-HMF), lack of specificity, and immunogenicity prevented further development.[20,21] Because a positive pharmacodynamic (PD) effect was observed with 20–30% Hb modification, this target modification is expected to provide therapeutic effect.

Voxelotor (previously GBT440) is a first-in-class therapy developed for the treatment of SCD by modulating the Hb affinity for oxygen. Voxelotor forms a reversible covalent bond with the N-terminal valine of the α-chain of Hb, resulting in an allosteric modification of Hb and eliciting an increase in oxygen affinity.[22] Because oxygenated HbS does not polymerize, Voxelotor may prevent sickling of RBCs and potentially interrupt the molecular pathogenesis of the disease. The new drug has the advantage of being available in oral formulation. Moreover, once-daily oral dosing has demonstrated linear pharmacokinetics with dose-dependent increases in haemoglobin-oxygen affinity. Also, Voxelotor is well tolerated with no dose-limiting toxicities or indications of tissue hypoxia.[23]

With estimable results of multiple clinical trials, the US Food and Drug Administration (FDA) in November 2019 approved Global Blood Therapeutic's Voxelotor (Oxbryta™) for the treatment of SCD in adults and paediatric patients 12 years of age or older.[24] The novel drug has proven to be a "breakthrough therapy" in the treatment of SCD in initial results promising to cater significant unmet needs of both the physicians and the society.

MECHANISM OF ACTION

Voxelotor is a HbS polymerization inhibitor that binds to HbS with a 1:1 stoichiometry. The drug is an oral small molecule designed to increase the oxygen affinity of HbS, shifting the oxygen dissociation curve of oxy-HbS to the left. Voxelotor acts by reversibly binding with the N-terminal valine of alpha (α) chain of haemoglobin, altering its conformational structure, thereby stabilizing the oxygenation form of the molecule. This leads to a reduction in the amount of deoxygenated HbS, the culprit molecule that polymerises to cause SCD.[25]

Nonclinical studies have also shown that Voxelotor may prevent sickling of RBC's and improve the RBC deformability, thereby leading to a reduction in blood viscosity.[25]

CLINICAL PHARMACOLOGY

Voxelotor is absorbed into plasma followed by preferential binding to RBCs. The drug is rapidly absorbed from the gastrointestinal tract after oral administration with median plasma and whole blood Tmax of the drug being approximately 2 hours. The absorption of the drug is increased when taken along with a high fat and a high caloric meal with an increase in AUC and Cmax by 42% and 45% respectively when compared to that in fasted state. Voxelotor has a high plasma protein binding being 99.8% in vitro and a blood to plasma ratio of approximately 15:1 in patients with SCD. The drug's apparent volume of distribution in the central and peripheral compartment are 338 lit and 72.2 lit in plasma, respectively. The peak concentrations in whole blood and RBCs are seen between 6 and 18 hours with a terminal half-life of 35.5 hours in patients of SCD. It is mainly metabolized by Phase I and II metabolisms, mediated primarily by CYP3A4 with major route of elimination in urine and faeces.[26]

Findings from the pharmacodynamic studies indicate that treatment with Voxelotor has a dose-dependent increase in Hb oxygen affinity as shown by the change in p50 (partial pressure of oxygen at which Hb oxygen saturation of 50% is achieved) that was linearly correlated with Voxelotor exposure. Also, the drug demonstrates a dose-dependent reduction in clinical measures of hemolysis (indirect bilirubin and % reticulocytes).[26]

DOSAGE, CLINICAL EFFICACY AND DRUG INTERACTIONS

Results of various dose response studies recommended a dosage of Voxelotor of 1,500 mg taken orally once daily with or without food. However, in patients of SCD with severe hepatic impairment (Child Pugh C), a dosage of 1000 mg is recommended to avoid hepatic injury. No dosage adjustment is required in patients with mild or moderate hepatic impairment.[27]

As metabolism of Voxelotor is primarily mediated by CYP3A4, administration of strong CYP3A4 inhibitors or flucanozole along with Voxelotor may increase the plasma concentrations of the later thereby leading to increased toxicity. Similarly, co-administration of strong CYP3A4 inducers along with Voxelotor may lead to decreased plasma concentration and reduced efficacy. As a result, concomitant use of strong or moderate CYP3A4 inducers, strong CYP3A4 inhibitors, or fluconazole with the drug should be avoided. However, in case they are to be given concomitantly, necessary dose adjustments should be done (Table 1).

Table 1: Voxelotor recommended dosage for concomitant medications.

Concomitant medication	Recommended Voxelotor dosage
Strong CYP3A4 inhibitors or fluconazole	1,000 mg once daily
Strong or moderate CYP3A4 inducers	2,500 mg once daily

CLINICAL TRIALS

The efficacy and safety of Voxelotor in sickle cell disease is derived from HOPE, a randomized, double-blind, placebo-controlled, multicenter trial (NCT 03036813). In this study, 274 patients were enrolled and randomized to daily oral administration of Voxelotor 1,500 mg (n=90), Voxelotor 900 mg (n=92), or placebo (n=92) (Figure 1).

Inclusion criteria included patients with 1 to 10 vaso-occlusive crisis (VOC) events within 12 months prior to enrollment and baseline hemoglobin (Hb) ≥5.5 to ≤10.5 g/dl. Eligible patients on stable doses of hydroxyurea for at least 90 days were allowed to continue hydroxyurea therapy throughout the study. Randomization was stratified by patients already receiving hydroxyurea (yes, no), geographic region (North America, Europe, Other), and age (12 to <17 years, 18 to 65 years). The trial excluded patients who received red blood cell (RBC) transfusions within 60 days and erythropoietin within 28 days of enrollment, had renal insufficiency, uncontrolled liver disease, were pregnant, or lactating. The majority of patients had HbSS or HbS/beta0-thalassemia genotype (90%) and were receiving background hydroxyurea therapy (65%). The median age was 24 years (range: 12 to 64 years); 46 (17%) patients were 12 to <17 years of age. Median baseline Hb was 8.5 g/dl (5.9 to 10.8 g/dl). One hundred and fifteen (42%) had 1 VOC event and 159 (58%) had 2 to 10 events within 12 months prior to enrollment.[27]

Efficacy was based on Hb response rate defined as a Hb increase of >1 g/dl from baseline to week 24 in patients treated with Voxelotor 1,500 mg versus placebo. The response rate for Voxelotor 1,500 mg was 51.1% (46/90) compared to 6.5% (6/92) in the placebo group (p<0.001). Additional efficacy evaluation included change in Hb and percent change in indirect bilirubin and percent reticulocyte count from baseline to Week 24 (Table 2).[27]

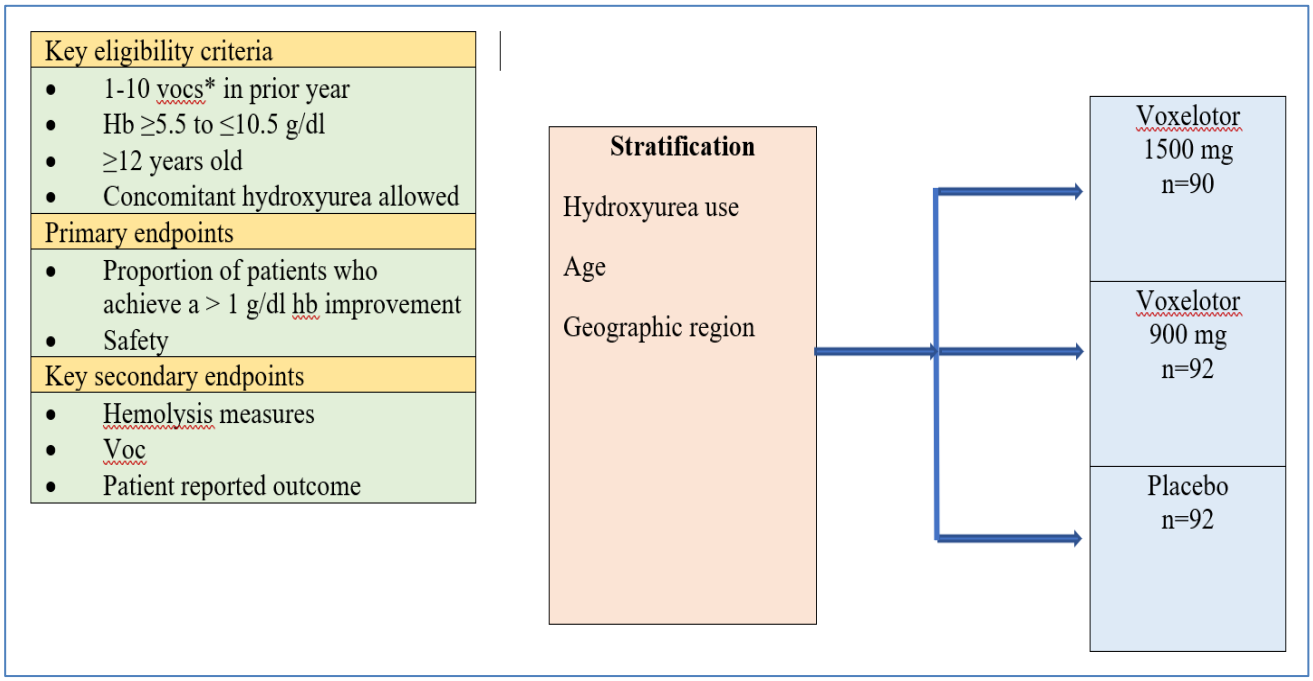

Figure 1: HOPE trial study design.

*Voc: Vaso-occlusive crisis.

Table 2: Adjusted mean (SE) change from baseline to week 24 in hemoglobin and clinical measures of hemolysis.

	Voxelotor 1500 mg (n=90) (%)	Placebo (n=92) (%)	P value
Hemoglobin (g/dl)	1.14 (0.13)	-0.08 (0.13)	<0.001
Indirect bilirubin	-29.08 (3.48)	-3.16 (3.52)	<0.001
Percent reticulocyte count	-19.93 (4.60)	4.54 (4.60)	<0.001

SAFETY AND ADVERSE DRUG REACTIONS

The safety of Voxelotor was evaluated in the phase 3 clinical trial (HOPE trial). The most common adverse reactions occurring in ≥10% of patients treated with Voxelotor 1,500 mg with a difference of >3% compared to placebo are summarized (Table 3). Modification of dosage (dose reduction or dosing interruption) due to an adverse reaction was done in 41% of patients who received Voxelotor Most frequent adverse reactions requiring dosage interruption included diarrhea, headache, rash, and vomiting. However, serious adverse reactions occurred in 3% of patients receiving the drug, which included headache, drug hypersensitivity, and pulmonary embolism occurring in 1 patient each.[27]

Table 3: Adverse reactions in patients receiving Voxelotor compared to placebo in HOPE.

Adverse reaction[a]	Voxelotor 1500 mg (n=88) (%)	Placebo (n=91) (%)
Headache	23 (26)	20 (22)
Diarrhea	18 (20)	9 (10)
Abdominal pain[b]	17 (19)	12 (13)
Nausea	15 (17)	9 (10)
Fatigue	12 (14)	9 (10)
Rash[c]	12 (14)	9 (10)
Pyrexia	11 (12)	6 (7)

[a]Adverse reactions were Grades 1 or 2 except for Grade 3 diarrhea (1), nausea (1), rash (1), and rash generalized (3).
[b]Abdominal pain (grouped PTs) included the following PTs: abdominal pain and upper abdominal pain.
[c]Rash (grouped PTs) includes the following PTs: rash, urticaria, generalized rash, maculo-papular rash, pruritic rash, papular rash, erythematous rash, and vesicular rash.

CONCLUSION AND PLACE IN THERAPY

The current decade has witnessed widespread interest in sickle cell research helping the physicians who can now offer hope to the many individuals living with this disorder around the world. A number of new sickle cell therapeutic options including gene therapy, stem cell transplantation and polymerization inhibitors are on the horizon. While most studies focused on preventing polymerization of the sickle erythrocyte have involved the use of drugs that could turn back the hands of the clock and switch on the production of haemoglobin F, Voxelotor has evolved as a novel pioneer in this regard, generating considerable excitement in the management of SCD. The initial clinical trial results of the drug have been promising. However, many more clinical trials need to be initiated and subjected to more strenuous examination and analysis than have been used in the past. Moreover, efforts will have to be made to offer these therapies in less advanced countries where the majority of individuals with sickle cell disease live.

Also, the feasibility of combination therapy including traditional and novel emerging therapeutics needs to be studied. This calls for an urgent debate with regards to the correct combinations, the right patient phenotype and access for the majority of patients.

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