JIMGS
Journal for International Medical Graduates

Volume 10 (07)
Accepted: December 22nd, 2025
Published: December 22nd, 2025
Review

Advancements in Sickle Cell Disease Treatment: A Review of Crizanlizumab

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Journal for International Medical Graduates

Abstract:

Sickle cell disease (SCD) is a chronic, inherited blood disorder marked by the presence of abnormal hemoglobin, which causes red blood cells to assume a rigid, sickle-like shape. These distorted cells contribute to hemolysis, impaired blood flow, and recurrent vaso-occlusive crises (VOCs), the hallmark and most debilitating complication of the disease. Beyond acute pain episodes, Sickle cell disease leads to progressive organ damage and reduced life expectancy, placing a substantial burden on patients and healthcare systems worldwide. While supportive care has long been the cornerstone of management, the emergence of targeted therapies offers new hope. Crizanlizumab, a humanized monoclonal antibody directed against P-selectin, disrupts the cellular adhesion processes that drive vaso-occlusive crises. This review highlights the pathophysiology of Sickle cell disease, details the mechanism of action of crizanlizumab, and evaluates clinical trial evidence regarding its efficacy, safety, and therapeutic potential. Collectively, the findings underscore crizanlizumab's promise as a transformative therapy that can reduce VOC frequency and improve quality of life for individuals living with SCD.

Key words: Sickle Cell Disease (SCD); Crizanlizumab, Vaso-occlusive crises (VOCs), P-selectin, Endothelial adhesion, Targeted therapy, Monoclonal antibody, Clinical trials, Safety profile, Voxelotor, L-glutamine, Novel therapeutics, Disease management,; Quality of life.

Introduction:

Sickle cell disease (SCD) is one of the most common inherited blood disorders worldwide, with an estimated 100,000 affected individuals in the United States and a projected global burden of more than 14 million births between 2010 and 2050[1]. In the United States, the disease disproportionately affects individuals of African, Mediterranean, Middle Eastern, and Indian ancestry, with the highest prevalence among African Americans, where approximately 1 in 365 births are affected[2]. Carrier status is also common, with about 1 in 13 African American infants born with sickle cell trait[3]. While newborn screening programs and advances in comprehensive care have improved survival, patients continue to experience considerable health challenges across their lifespan, underscoring the ongoing public health burden.

At its core, Sickle cell disease is a genetic disorder caused by a point mutation in the β-globin gene that produces hemoglobin S[4]. When deoxygenated, hemoglobin S polymerizes, distorting normally pliable red blood cells into a rigid, crescent or "sickle" shape. These sickled cells are prone to hemolysis, reduced oxygen delivery, and vascular occlusion. The consequences are far-reaching: chronic hemolytic anemia, recurrent vaso-occlusive crises (VOCs), and progressive organ damage that collectively drive significant morbidity and premature mortality[5].

Vaso-occlusive crises, in particular, are the hallmark of SCD and one of its most debilitating clinical manifestations. They present as severe, acute pain episodes often requiring emergency department visits, hospitalization, and intensive analgesic therapy[5]. In 2006, over 230,000 emergency department visits in the United States were attributed to SCD, with 81% occurring in adults and the remainder in pediatric patients. Moreover, the frequency of vaso-occlusive crises is strongly linked with diminished quality of life and adverse clinical outcomes[6].

Despite decades of research, traditional management of Sickle cell disease has largely relied on supportive measures and symptomatic relief rather than targeted interventions. The introduction of hydroxyurea represented a major step forward, but limitations remain[7]. Recently, novel targeted therapies have emerged, offering new hope for disease modification. Among these- Crizanlizumab, a monoclonal antibody against P-selectin has demonstrated efficacy in reducing vaso-occlusive crises[8]. Alongside Crizanlizumab, Voxelotor and L-glutamine have also been approved by the U.S. Food and Drug Administration (FDA), expanding the therapeutic armamentarium available to clinicians[9].

This review summarizes the pathophysiology of Sickle cell disease, discusses the mechanism of action of Crizanlizumab, and evaluates the clinical trial evidence supporting its role in the prevention of vaso-occlusive

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crises with attention to safety, tolerability, and future therapeutic implications.

Pathophysiology of Sickle cell disease:

The pathophysiology of sickle cell disease (SCD) is multifactorial, involving abnormal hemoglobin, altered red blood cell morphology, endothelial dysfunction, and inflammatory processes. The underlying defect arises from hemoglobin S, which polymerizes under low oxygen conditions[10]. This causes red blood cells to adopt a rigid, sickle shape, making them less deformable and more prone to hemolysis.

Beyond hemolysis, sickled red blood cells interact abnormally with the vascular endothelium, leukocytes, and platelets, triggering inflammation and vascular injury[5]. Central to the pathogenesis of vaso-occlusive crises (VOCs) is the adhesion of sickled red blood cells to the vascular endothelium, which leads to microvascular occlusion, tissue ischemia, and pain[5]. A critical factor in this adhesion process is the upregulation of endothelial adhesion molecules such as P-selectin, which facilitates binding between sickle red blood cells, leukocytes, and the vessel wall.

Role of P-Selectin in Vaso-occlusion:

P-selectin is a cell adhesion molecule expressed on activated endothelial cells and platelets. It plays a pivotal role in the initiation and propagation of VOCs by mediating the tethering and rolling of sickle red blood cells and leukocytes along the endothelium. This interaction promotes firm adhesion, microvascular occlusion, and subsequent tissue ischemia[9].

Through these mechanisms, P-selectin acts as a central mediator of the "stickiness" that drives vascular obstruction, inflammation, and the hallmark acute pain episodes of SCD. Its contribution to both cellular adhesion and endothelial dysfunction makes it an important therapeutic target in the management of VOCs[9].

Mechanism of action of Crizanlizumab:

Crizanlizumab is a humanized monoclonal antibody that specifically binds to P-selectin, blocking its interaction with ligands on sickled red blood cells and leukocytes[11]. By preventing these adhesion events, crizanlizumab interrupts the cascade that leads to vascular obstruction, thereby reducing the frequency and severity of VOCs.

During VOCs, sickle-shaped red blood cells become abnormally adhesive, obstructing blood flow in small vessels and causing ischemia, inflammation, and acute pain. By inhibiting P-selectin, crizanlizumab prevents this adhesion, helping maintain blood flow and vascular integrity[12].

Beyond reducing VOC frequency, crizanlizumab may also limit downstream complications associated with endothelial dysfunction and vascular injury, such as acute chest syndrome and stroke. Overall, its targeted mechanism provides a novel therapeutic strategy for improving outcomes and quality of life in patients with SCD[13].

Clinical trials:

Several key clinical trials have evaluated the efficacy and safety of crizanlizumab in patients with sickle cell disease (SCD), ranging from adults to pediatric populations. These studies have provided critical evidence supporting its role in reducing the frequency and severity of vaso-occlusive crises (VOCs).

SUSTAIN Trial (Phase II)
The SUSTAIN trial was a randomized, double-blind, placebo-controlled Phase II study designed to evaluate the efficacy of crizanlizumab in patients with SCD. The primary endpoint was the annual rate of VOCs requiring medical care. Results demonstrated a significant reduction in the median annual rate of VOCs among patients receiving crizanlizumab compared to those on placebo, highlighting the drug's potential to reduce disease burden[14].

HOPE Trial (Phase III)
The HOPE trial was a large, randomized, double-blind, placebo-controlled Phase III study involving patients with SCD. The primary endpoint was the annual rate of VOCs requiring healthcare visits. Consistent with findings from the SUSTAIN trial, crizanlizumab significantly reduced the median annual rate of VOCs compared to placebo, reinforcing its clinical efficacy in preventing recurrent painful episodes[14].

HOPE-KIDS 1 Trial (Phase II)
The HOPE-KIDS 1 trial was an open-label, single-arm Phase II study conducted in pediatric patients aged 6–17 years with SCD. The primary objective was to assess the incidence of treatment-emergent adverse events (TEAEs). Results demonstrated that crizanlizumab was generally safe and well tolerated, providing important safety and dosing data in the pediatric population[14].

SUSTAIN 1 and SUSTAIN 2 Extension Trials (Phase II)
Both SUSTAIN 1 and SUSTAIN 2 Extension trials are open-label extension studies involving patients who previously completed the SUSTAIN trial. These studies aim to evaluate the long-term safety, tolerability, and efficacy of crizanlizumab. The primary endpoints include the incidence of adverse events and the annual rate of VOCs. Both trials remain ongoing and are expected to offer valuable insights into the sustained benefits of crizanlizumab over extended treatment periods[14].

HOPE-KIDS 3 Trial (Phase II)
The HOPE-KIDS 3 trial is an open-label Phase II study enrolling very young pediatric patients aged 1 to <2 years with SCD. The study's primary endpoint is the incidence of treatment-emergent adverse events. This ongoing trial seeks to determine the safety profile of

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crizanlizumab in early childhood and expand its therapeutic applicability to younger age groups[14].

SOLACE Trial (Phase III)
The SOLACE trial is a randomized, double-blind, placebo-controlled Phase III study designed to assess the effect of crizanlizumab in patients with SCD and a history of VOCs. The primary endpoint is the time to first VOC. Preliminary results suggest that crizanlizumab reduced the time to first VOC compared to placebo, further supporting its benefit in VOC prevention[15].

Clinical Trial	Phase	Design	Population	Primary Endpoints	Results
SUSTAIN Trial	II	Randomized, double-blind, placebo-controlled	Patients with SCD	Annual rate of VOCs requiring medical care	Significant reduction in median annual rate of VOCs with crizanlizumab vs. placebo [14,16]
HOPE Trial	III	Randomized, double-blind, placebo-controlled	Patients with SCD	Annual rate of VOCs requiring healthcare visits	Significant reduction in median annual rate of VOCs with crizanlizumab vs. placebo [17]
HOPE-KIDS 1 Trial	II	Open-label, single-arm	Pediatric patients with SCD (6-17)	Incidence of treatment-emergent adverse events (TEAEs)	Provided safety and tolerability data in pediatric population [17]
HOPE-KIDS 2 Trial	II	Open-label, single-arm	Pediatric patients with SCD (<6)	Incidence of TEAEs	Ongoing
SUSTAIN 2 Trial	II	Open-label extension	Patients who completed SUSTAIN	Incidence of adverse events; annual rate of VOCs	Ongoing
SUSTAIN 1 Extension	II	Open-label extension	Patients who completed SUSTAIN	Incidence of adverse events; annual rate of VOCs	Ongoing
HOPE-KIDS 3 Trial	II	Open-label	Pediatric patients with SCD (1-<2)	Incidence of TEAEs	Ongoing
SOLACE Trial	III	Randomized, double-blind, placebo-controlled	Patients with SCD and a history of VOCs	Time to first VOC	Reduction in time to first VOC compared to placebo [15]

Among the clinical trials conducted, the *SUSTAIN trial* stands out as a pivotal Phase II study that established the clinical promise of Crizanlizumab in the management of sickle cell disease (SCD)[14]. In this randomized, double-blind, placebo-controlled trial, patients with SCD were enrolled to evaluate the effect of Crizanlizumab on the annual rate of vaso-occlusive crises (VOCs) requiring medical care[13]. The study demonstrated a significant reduction in the median annual rate of VOCs in patients treated with Crizanlizumab compared to those receiving placebo, underscoring its potential as an effective prophylactic therapy for VOCs[18].

Building upon these findings, the *HOPE trial*, a Phase III randomized, double-blind, placebo-controlled study, further confirmed the efficacy of crizanlizumab in reducing the frequency of VOCs requiring healthcare visits. The results paralleled those of the *SUSTAIN trial*, showing a significant reduction in VOC frequency, thereby reaffirming Crizanlizumab's role in VOC prevention and overall disease management[16]. Collectively, these clinical trials provide strong evidence supporting the use of Crizanlizumab as a promising therapeutic option to reduce the burden of VOCs and improve quality of life in patients with SCD.

In addition to Crizanlizumab, other agents such as L-glutamine and Voxelotor have also been approved by the U.S. Food and Drug Administration (FDA) for the treatment of SCD and prevention of VOCs. Voxelotor is an oral, small-molecule inhibitor of hemoglobin polymerization that helps prevent the sickling of red blood cells[17]. It has been evaluated in multiple clinical trials, including the *HOPE, HOPE-KIDS, and HOPE-KIDS 2* studies, demonstrating its ability to increase hemoglobin levels, reduce hemolysis, and lower VOC frequency in patients with SCD[16].

L-glutamine, an amino acid precursor of nicotinamide adenine dinucleotide (NAD), has been shown to decrease oxidative stress, improve red blood cell hydration, and reduce sickling. Phase II and Phase III studies, including the L-Glutamine Therapy for Sickle Cell Anemia and Sickle β^0 Thalassemia (STOP) trial, have reported reductions in VOC frequency and hospitalization rates, further supporting its clinical utility[14].

While Crizanlizumab, Voxelotor, and L-glutamine have each demonstrated clinical benefits, they differ in their mechanisms of action and target pathways[19]. Crizanlizumab primarily prevents vascular adhesion by inhibiting P-selectin; Voxelotor acts at the molecular level to stabilize hemoglobin; and L-glutamine works through metabolic and antioxidant effects. Understanding these distinctions allows healthcare providers to tailor therapy based on patient-specific factors, disease severity, and treatment goals[17].

The recommended dose of Crizanlizumab is 5 mg/kg, based on actual body weight. The drug is supplied as a 100 mg/10 mL single-dose vial, which should be diluted

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to a total volume of 100 mL with either 0.9% sodium chloride or 5% dextrose and administered as an intravenous infusion over 30 minutes[20]. Treatment involves an initial dose, a second dose two weeks later, and subsequent doses every four weeks. Long-term extension studies have shown sustained clinical benefits and a favorable safety profile with continued therapy, supporting its role as a viable long-term treatment for patients with SCD[13].

Safety and cost profile of Crizanlizumab:

The safety profile of Crizanlizumab has been generally favorable across clinical studies, with most adverse events reported as mild to moderate in severity. The most common adverse reactions include headache, arthralgia, nausea, and pyrexia**,** which were typically self-limiting and did not necessitate discontinuation of therapy. Importantly, no significant differences in the incidence of serious adverse events or infections were observed between the Crizanlizumab and placebo groups in either the *SUSTAIN or HOPE trials*, indicating a comparable safety profile to standard care[9].

From an economic perspective, the cost of Crizanlizumab presents a considerable factor in treatment planning. In the United States, the estimated price is approximately $2,357 per 100 mg/10 mL vial, and a typical dose regimen requires four vials per infusion based on body weight. This represents a substantial financial burden for both patients and healthcare systems, underscoring the importance of cost-effectiveness analyses and equitable access considerations when incorporating Crizanlizumab into clinical practice[9].

Conclusion:

Crizanlizumab represents a major advancement in the therapeutic landscape of sickle cell disease (SCD), providing a targeted and disease-specific approach to the prevention of vaso-occlusive crises (VOCs)—a defining and debilitating feature of SCD. By inhibiting P-selectin–mediated adhesion of sickled red blood cells and leukocytes to the vascular endothelium, crizanlizumab effectively reduces the frequency of VOCs and contributes to improved patient quality of life**.**
While current evidence highlights its efficacy and favorable safety profile, continued research is essential to better understand its long-term outcomes**,** cost-effectiveness, and potential benefits when used in combination with other emerging therapies such as Voxelotor and L-glutamine. Overall, Crizanlizumab holds significant promise as a transformative therapy, marking a pivotal step toward improving clinical outcomes and advancing personalized care in patients with sickle cell disease.

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Accepted: December 22nd, 2025
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