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Crizanlizumab for the Prevention of Vaso-Occlusive Pain Crises in Sickle Cell Disease

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Abstract

Objective: To review the efficacy and safety of crizanlizumab (Adakveo) in the prevention of vaso-occlusive pain crises in sickle cell disease. **Data Sources:** An English-language literature search of PubMed, MEDLINE, and Ovid (1946 to January 2021) was completed using the terms crizanlizumab, SEG101, SelG1, and sickle cell disease. Manufacturer prescribing information, article bibliographies, and data from clinicaltrials.gov were incorporated in the reviewed data. **Study Selection/Data Extraction:** All studies registered on clinicaltrials.gov were incorporated in the reviewed data. **Data Synthesis:** Crizanlizumab is the first monoclonal antibody approved for sickle cell disease to reduce the frequency of vaso-occlusive crises. One phase 2 clinical trial and a post hoc analysis of the trial have been published. **Relevance to Patient Care and Clinical Practice:** Crizanlizumab is a monthly intravenous infusion approved by the Food and Drug Administration for patients with sickle cell disease 16 years of age and older to reduce the frequency of vaso-occlusive crises. **Conclusion:** Crizanlizumab appears to be an efficacious therapy for patients with sickle cell disease to reduce the frequency of vaso-occlusive crises. Concerns include drug cost and administration. Long-term benefits and risks have not been determined.

Keywords

crizanlizumab, Adakveo, sickle cell disease

Introduction

Sickle cell disease (SCD) is a genetic condition where the expression of an abnormal sickle hemoglobin (HbS) gene alters the shape and function of erythrocytes. The abnormal gene can be homozygous for HbS or in a combination of one HbS gene with either hemoglobin C or β-thalassemia.[1] It is estimated that SCD is present in about 100 000 people in the United States, but is projected to affect over 14 million births worldwide between 2010 and 2050.[1,2] Both life expectancy and quality of life are affected by SCD.[1]

The HbS-containing erythrocyte changes into a sickled shape after deoxygenation of the hemoglobin, resulting in hemolysis, anemia, and vessel occlusion.[1] During hemolysis, a complex pathway increases the activity of adhesion molecules that promote intercellular and endothelial adhesion.[3] Hemoglobin released from hemolyzed erythrocytes scavenges nitric oxide, a molecule that typically prevents cellular adhesion.[4] During this phase, nitric oxide–sustained vasodilation decreases and platelets are activated, expressing selectin molecules and other adhesion modulators. The endothelium also expresses selectin, increased due to inflammatory damage through interactions with heme.[4] Release of these selectins encourage cellular adhesion, promoting vaso-occlusion.[4,5] Neutrophils, platelets, and mast cells also adhere to the erythrocytes, contributing to vessel occlusion.[6] Multiple organ systems are affected, but the acute complications of SCD directly result from ischemia of tissues, leading to infections, acute chest syndrome (ACS), potential organ failure, and vaso-occlusive crisis (VOC).[1]

A VOC is an acutely painful episode that frequently results in emergency department visits and extended hospital stays.[7] Additionally, quality of life is inversely correlated with VOC frequency.[6] In 2006, it was estimated that of the over 230 000 visits to the emergency department in the United States for SCD, 81% were in adults with the remainder in pediatric patients.[7] Using a Medicaid database, Shah et al estimated that adults with SCD experience approximately 3 VOCs a year with the length of hospital stay ranging from 7 to 10 days, consistent with other estimates.[6,8]

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While the treatment of VOC focuses on multimodal analgesia, prevention is an area of pharmacotherapy that has few options. The American Society of Hematology published guidelines in 2020 addressing the management of acute and chronic pain. However, the concept of prevention was not a major focus.[9] In the guidelines for the management of SCD published by the National Heart, Lung, and Blood Institute in 2014, hydroxyurea was the only pharmacologic recommendation to reduce the frequency of VOC.[10] Since then, L-glutamine, voxelotor, and crizanlizumab have been approved by the Food and Drug Administration (FDA) for treatment of SCD and prevention of VOC.[11]

Approved in November 2019, crizanlizumab-tmca is a humanized immunoglobulin G2 monoclonal antibody that blocks the interaction of P-selectin on the surface of the endothelium and platelets with erythrocytes and leukocytes.[3,12] It is approved for use in patients aged 16 years and older and is administered by intravenous (IV) infusion over 30 minutes, initially every 2 weeks and then every 4 weeks.[12] As this is a novel agent for the management of SCD, it plays an important role in the prevention of VOC. An overview of crizanlizumab is discussed in this article.

Data Selection

An English-language literature search of PubMed, MEDLINE, and Ovid (1946 to January 2021) was completed using the terms crizanlizumab, SEG101, SelG1, and sickle cell disease. Two authors independently completed the literature review, with all authors involved in literature selection. Manufacturer prescribing information and article bibliographies were also incorporated for additional materials. All studies registered on clinicaltrials.gov were included in the reviewed data. Studies involving crizanlizumab for disease states other than SCD were not included as part of this review. Only trials with published data were discussed in detail. Those trials with abstracts only were included in Table 1.

Pharmacology

Crizanlizumab is an immunoglobulin G2 kappa monoclonal antibody that binds to P-selectin, blocking its interaction with P-selectin glycoprotein ligand 1 (PSGL-1).[12] Endothelial selectins, both E-selectin and P-selectin, are believed to play a large role in the development of VOC.[13,14] Mice studies have shown that blockade of P-selectin decreases the adhesion of sickled red blood cells.[13] P-selectin upregulation in endothelial cells and platelets in those with SCD appears to contribute significantly to the development of VOC.[14] By blocking the interaction with P-selectin ligands, crizanlizumab decreases the adhesion of erythrocytes, leukocytes, platelets, and endothelial cells, thereby reducing the likelihood of vaso-occlusion.

Pharmacokinetics

The pharmacokinetic (PK) outcomes of crizanlizumab are based on data found in both healthy volunteers and subjects with SCD.[12,15] At the FDA-approved dose of 5 mg/kg, the mean crizanlizumab C_{max}, area under curve $(AUC)_{last}$, and AUC_{inf} are 0.16 mg/mL, 33.6 mg*h/mL, and 34.6 mg*h/mL, respectively. Volume of distribution of crizanlizumab is 4.26 L. The mean terminal elimination half-life is 10.6 days, with a clearance of 11.7 mL/h in healthy volunteers. In patients with SCD, the mean terminal elimination half-life is shortened to 7.6 days. Metabolism of crizanlizumab is proposed to occur via catabolic pathways. At this time, the effect of renal or hepatic impairment on the PK of crizanlizumab is unknown.

Ataga et al evaluated the pharmacokinetics, pharmacodynamics, and immunogenicity of crizanlizumab.[14] Serum crizanlizumab concentrations remained in therapeutic range for the 52-week treatment period after the initial loading doses (2 doses 2 weeks apart).[14] During the maintenance phase, mean troughs were 2.8 to 6.8 μg/mL with low-dose crizanlizumab and 10.5 to 15 μg/mL with high-dose crizanlizumab.[14] High-dose crizanlizumab (5 mg/kg) successfully blocked P-selectin binding to PSGL-1, whereas the low-dose regimen (2.5 mg/kg) achieved only partial blockade. Crizanlizumab antibodies were not detected.[14]

Clinical Trials

A number of clinical trials examining crizanlizumab in the treatment of SCD are either ongoing or complete. Table 1 describes 9 studies including clinical trial identifier, enrollment status, study design, patient ages, and the primary/secondary outcomes for each trial.[14,16-18] To date there are 2 peer-reviewed publications of crizanlizumab trial data, both reporting data from the SUSTAIN study.[14,16] These are both described in detail below. Other studies listed in Table 1 do not currently have any published trial data.

Phase 2 Trial: SUSTAIN

SUSTAIN (NCT01895361) is a double-blind, randomized, placebo-controlled, phase 2 trial of crizanlizumab in patients 16 to 65 years of age with SCD.[14] SCD was described in the study as HbSS, HbSC, $HbS\beta^0$-thalassemia, $HbS\beta^+$-thalassemia, or other genotypes. To be eligible, patients had to have experienced 2 to 10 VOCs in the previous 12 months as determined by medical history or patient's recall. Concomitant hydroxyurea use was allowed, but patients must have been receiving it for at least 6 months and on a stable dose for 3 months before enrollment. No dose changes in hydroxyurea were allowed except if necessary for patient safety. Initiating hydroxyurea during the study period was not allowed. Patients on long-term red-cell infusion therapy were excluded.

Table 1. Crizanlizumab Clinical Trials.[14,16-18]

National clinical trial identifier	Trial name	Enrollment status	Study phase/trial type	Patient ages	Primary outcome measures	Select secondary outcome measures
NCT01895361	SUSTAIN	Completed[13,14]	Phase 2, randomized, placebo-controlled, double-blind	16 to 65 years	Annual rate of sickle cell-related pain crises	Health care visit data, sickle cell-related pain crisis data, and acute chest syndrome rates
NCT03264989	SOLACE-adults	Active, not recruiting	Phase 2, open-label	16 to 70 years	PK and PD measurements	VOC rates and events, health care visit data
NCT03474965	SOLACE-kids	Recruiting	Phase 2, open-label	6 months to <18 years	PK, PD, and safety measurements	VOC rates, health care visit data, adverse events, hemoglobin, growth/ sexual maturity, anti-drug antibodies, and PK profiles
NCT03814746	STAND	Recruiting	Phase 3, randomized, placebo-controlled, double-blind	≥12 years	Rate of VOC events leading to health care visit	Health care visit data, PK profiles, hemoglobin, growth/sexual maturity, and anti-drug antibodies
NCT03938454	SPARTAN	Recruiting	Phase 2, open-label	Males ≥16 years	Percent change in priapic events from baseline	Priapic event rates, VOC data
NCT04053764	STEADFAST	Recruiting	Phase 2, randomized, open-label	≥16 years	Percentage of patients with ≥30% decrease in albuminuria	Albuminuria, protein to creatinine ratio, estimated glomerular filtration rate, anti-drug antibodies, PK profiles, and health care visit data
Not available	SUCCESSOR	Ongoing[15]	Retrospective, non-interventional follow-up study of adult patients in SUSTAIN	≥18 years	Evaluate outcomes related to sickle cell disease	Evaluate outcomes related to sickle cell disease
NCT04662931	—	Not yet recruiting	Phase 4, open-label	≥16 years	Serious adverse events	Adverse events
NCT04657822	—	Not yet recruiting	Phase 4, open-label, rollover	Any age; rollover from previous studies	Adverse events	—

Abbreviations: PK, pharmacokinetic; PD, pharmacodynamic; VOC, vaso-occlusive crisis.

The trial included a 30-day screening phase, 52-week treatment phase, and 6-week follow-up assessment phase. Patients were randomized using a block design, with stratification based on the number of crises in the previous year and concomitant hydroxyurea use. Patients were assigned in a 1:1:1 ratio to low-dose crizanlizumab (2.5 mg/kg), high-dose (5 mg/kg), or placebo. Two loading doses of the study drug or placebo were given 2 weeks apart followed by maintenance doses every 4 weeks through week 50. Fourteen total doses were administered. Efficacy, safety, and PK assessments were completed at dose 1, 2 weeks later, every 4 weeks to week 50, and at week 52. The final data collection point was 8 weeks after the final dose.

The annual rate of VOCs was the primary efficacy end point. A crisis, defined as a vaso-occlusive event requiring treatment, ACS, hepatic sequestration, splenic sequestration, or priapism, was further adjudicated by an independent, blinded crisis-review committee. Secondary efficacy markers included time to first and second crisis, a pain assessment, annual rate of days hospitalized, uncomplicated crises, and ACS. Pharmacokinetics and pharmacodynamics were evaluated at baseline and at subsequent trial visits. Patient safety was also monitored throughout the study. Safety assessments included physical examination, vital signs, clinical laboratory tests, 12-lead electrocardiogram, and assessment of immunogenicity. Statistical analysis was completed according to the intention-to-treat principle. Enrollment of at least 50 patients per treatment group was determined to be necessary for >90% power with α of .05.

Over 18 months, 198 patients at 60 locations in the United States, Brazil, and Jamaica were randomly assigned to receive high-dose crizanlizumab (67 patients), low-dose crizanlizumab (66 patients), or placebo (65 patients). Baseline characteristics were similar across groups. The median age (in years) for groups were as follows: 29 (high-dose crizanlizumab), 29 (low-dose crizanlizumab), and 26 (placebo). Participants with HbSS genotype comprised 70% (n = 47) of the high-dose group, 71% (n = 47) of the low-dose group, and 72% (n = 47) of the placebo group. Rate of concomitant hydroxyurea use was 63% (n = 42) in the high-dose group, 62% (n = 41) in the low-dose group, and 62% (n = 40) in the placebo group. Participants with 5 to 10 crises in the preceding year were 37% (n = 25) in the high-dose group, 38% (n = 25) in the low-dose group, and 37% (n = 24) in the placebo group. Other baseline characteristics included sex, race, and baseline laboratory values. Sixty-nine participants discontinued the trial early, but reasons were comparable among the 3 groups. Common categories for early dropouts included withdrawal by the subject, patient lost to follow-up, or other. Where more specific information was provided, the most prevalent explanations given for discontinuation included pregnancy, difficult venous access, and patient relocation. One patient from the high-dose group, one patient from the low-dose group, and 3 patients in the placebo group withdrew from the trial due to adverse effects.

Following the treatment phase, the median VOC rate per year in the high-dose crizanlizumab group compared with placebo was 1.63 versus 2.98, indicating a 45.3% lower rate with high-dose crizanlizumab (P = .01). In the low-dose crizanlizumab group, the median yearly VOC rate was 2.01, a 32.6% lower rate than placebo (P = .18). A number of patients, 36% (n = 24) in high-dose crizanlizumab, 18% (n = 12) in low-dose crizanlizumab, and 17% (n = 11) in the placebo group, did not have a VOC during the treatment phase. Annual VOC rates were analyzed in the subgroups of concomitant hydroxyurea use, history of VOC frequency, and SCD genotype. The median annual VOC rate in those receiving concomitant hydroxyurea therapy was 2.43 in the high-dose crizanlizumab versus 3.58 in the placebo group, representing a 32.1% lower rate. The positive benefit of high-dose crizanlizumab remained consistent with history of crisis frequency and SCD genotype.

Regarding secondary end points, the median days hospitalized was lower in the high-dose crizanlizumab group (4 days with interquartile range of 0-25.72) compared with placebo (6.87 days with interquartile range 0-18), but this difference was not statistically significant (P = .45). However, the median times to both first and second VOC were found to be statistically significantly longer in those on high-dose crizanlizumab versus those receiving placebo (4.07 vs 1.38 months, P = .001; and 10.32 vs 5.09 months, P = .02, respectively). Of importance, the lower VOC frequency in the high-dose crizanlizumab cohort was evident at week 2 and was maintained throughout the 52-week treatment phase. Median time to VOC in the low-dose crizanlizumab group did not significantly differ from placebo. The high-dose crizanlizumab group was found to have a 62.9% lower rate of uncomplicated crises per year compared with placebo (median rate, 1.08 vs 2.91; P = .02). ACS, hepatic or splenic sequestration, and priapism were rare in all groups (median rate = 0.00). Quality of life assessments utilizing the Brief Pain Inventory questionnaire revealed no significant changes in pain-severity and pain-interference domains during the trial.

Serious adverse events occurred in the high-dose crizanlizumab (n = 17), low-dose crizanlizumab (n = 21), and placebo groups (n = 17) in similar numbers. Five patients died during the trial with 2 being in the high-dose cohort (ACS and endocarditis/sepsis). The most frequent serious adverse events were pyrexia (2 patients in high-dose, 0 in low-dose, and 1 in placebo groups), influenza (3 patients in low-dose, 0 in high-dose, or placebo groups), and pneumonia (3 in high-dose, 2 in low-dose, and 3 in placebo). Adverse events occurring in ≥10% of patients receiving either low-dose or high-dose crizanlizumab included headache, back pain, nausea, arthralgia, pain in limbs, urinary tract infection, pyrexia, diarrhea, musculoskeletal pain, pruritus,

vomiting, and chest pain. Because the length of the trial was 52 weeks, data regarding safety, efficacy, and the potential development of antibodies to crizanlizumab beyond trial length are unknown. An additional limitation of the trial is the significant amount of patient dropouts, which may have affected the treatment results.

Subgroup Analysis: SUSTAIN

Kutlar et al present a post hoc subgroup analysis of the original phase 2 SUSTAIN study that evaluates the effect of high-dose crizanlizumab (5 mg/kg) versus placebo on safety assessments and certain secondary end points.[16] Low-dose crizanlizumab (2.5 mg/kg) was not included as it did not meet the primary end point of SUSTAIN. Patient characteristics reviewed include number of VOCs in the year prior to study entry, concomitant hydroxyurea use, and SCD genotype. Efficacy factors studied comprise proportion of VOC-free patients, time to first and second pain crisis, uncomplicated crisis events, and ACS. Safety evaluations collected the number of treatment-emergent adverse events and treatment-emergent serious adverse events. The number of VOC-free patients was greater in the crizanlizumab arm (35.8%, n = 24/67) compared with placebo (16.9%, n = 11/65). Crizanlizumab use was also associated with increased time to first and second crisis events versus placebo. Patients in the HbSS genotype subgroup had a time-to-first-crisis event of 4.07 months with crizanlizumab compared with 1.12 months (hazard ratio = 0.5; 95% confidence interval [CI] = 0.31-0.80) with placebo. Patients with 2 to 4 VOC events prior to enrollment had a time-to-first crisis event of 4.76 months with crizanlizumab versus 1.61 months with placebo (hazard ratio = 0.53; 95% CI = 0.31-0.9). Those with 5 to 10 VOC events had a time-to-first crisis event of 2.43 months compared with 1.03 months with placebo (hazard ratio = 0.47; 95% CI = 0.25-0.89). In the concomitant hydroxyurea subgroup, time to first event was 2.43 months with crizanlizumab versus 1.15 months with placebo (hazard ratio = 0.58; 95% CI = 0.35-0.96). In the nonconcomitant hydroxyurea subgroup, time to first event was also longer (5.68 vs 2.86 months; hazard ratio = 0.39; 95% CI = 0.20-0.76).

The median rate of uncomplicated SCD-related crisis events was found to be lower in the crizanlizumab arm versus placebo across all subgroups. In the hydroxyurea subgroup, the median rate of uncomplicated events was 1.74 (0-24.3) with crizanlizumab versus 3.13 (0-13.5) with placebo. Patients in the HbSS subgroup had a median rate of uncomplicated events of 1.63 (0-24.3) with crizanlizumab versus 3.00 (0-19.2) with placebo. Patients in the subgroup of 5 to 10 VOCs in the previous year had a median rate of uncomplicated events of 1.85 (0-24.3) with crizanlizumab versus 4.84 (0-19.2) with placebo. The incidence of complicated crisis types defined as ACS, hepatic or splenic sequestration, priapism requiring a medical visit, or death not from suicide, homicide, or accident, was too low for proper subgroup analysis. In the safety evaluation, the total rates of serious and nonserious adverse events were analogous. The subgroup analysis did identify higher rates of treatment-related adverse events and serious adverse events in patients receiving crizanlizumab across all subgroups, yet the incidence of adverse events leading to discontinuation was low in both arms (0% to 8% in crizanlizumab vs 0% to 8.7% in placebo). No patient deaths were linked to treatment-related adverse events. Because this is a post hoc analysis of subgroups from the SUSTAIN trial, any results must be interpreted with caution.

Ongoing/New Trials

There are numerous ongoing trials of crizanlizumab for the treatment of SCD that will provide evidence for use in the pediatric population as well as additional safety and efficacy data in adults (Table 1).[14,16-18] SUCCESSOR is a retrospective long-term follow-up of patients from the completed SUSTAIN trial. Two phase 2 open-label trials, SOLACE-adults and SOLACE-kids, are both examining pharmacokinetic and pharmacodynamic parameters. SOLACE-kids is also evaluating safety data in the pediatric population. SPARTAN is an open-label phase 2 trial examining crizanlizumab's effect on priapism events in SCD patients. STEADFAST is a phase 2 trial examining the effect of crizanlizumab on albuminuria in SCD. STAND, the only phase 3 trial, is examining the rate of VOC events in SCD patients 12 years of age and older. Two phase 4 trials are not yet recruiting. Finally, a managed access program is ongoing to allow treatment with crizanlizumab for patients with SCD.

Dosing, Administration, and Safety

The recommended dose of crizanlizumab is 5 mg/kg using the patient's actual body weight.[12] The medication is available as a single dose vial (100 mg/10 mL). The calculated dose is then diluted to a total volume of 100 mL with 0.9% sodium chloride or 5% dextrose. Administration is by IV infusion over 30 minutes.[12] The initial dose is administered followed by a second dose at 2 weeks, and then administered every 4 weeks.[12] Patients should be monitored for infusion-related reactions, and the infusion should be stopped for severe reactions. Symptoms of infusion-related reactions include fever, chills, nausea, vomiting, fatigue, dizziness, pruritus, urticaria, sweating, shortness of breath, or wheezing.[12] One case report describing a potential infusion-related reaction has been published thus far.[19] This case describes a 17-year-old male who developed severe acute pain within

10 minutes of the start of infusion requiring its discontinuation.[19] Persistent pain and fever required a 7-day hospitalization with no further rechallenge planned with crizanlizumab.[19] The only known interaction is with automated platelet counts in blood collection tubes containing ethylenediaminetetraacetic acid as crizanlizumab may interfere with results. Crizanlizumab is not recommended in pregnancy unless the expected benefit outweighs the potential risk to the fetus.[12] The safety and efficacy of crizanlizumab in patients younger than 16 years of age has not been established.[12] The most common adverse effects attributed to the medication include nausea, arthralgia, back pain, and fever.[15] Because crizanlizumab affects the recruitment of leukocytes, it is unknown if this affects infection risk.[20]

Relevance to Patient Care and Clinical Practices and Medication Cost

Crizanlizumab is the only monoclonal antibody approved to treat patients with SCD. Prior to 2019, the most common treatment for SCD was hydroxyurea. Lack of response in up to 25% of sickle cell patients, adherence, adverse effects, and laboratory monitoring may preclude the use of hydroxyurea.[11] L-glutamine, an amino acid believed to reduce oxidative stress of sickled erythrocytes, is also FDA approved to reduce VOCs in patients 5 years of age and older, but its use is limited by cost and compliance issues.[21] Voxelotor is approved in patients 12 years of age and older, and its mechanism involves the inhibition of HbS polymerization.[11] Mechanistically distinct, crizanlizumab and voxelotor were both approved by the FDA in November 2019 for the treatment of SCD. There are no comparative trials of l-glutamine, crizanlizumab, and voxelotor.

Crizanlizumab offers an alternative for patients who do not tolerate or fail hydroxyurea.[20] As the SUSTAIN trial included both patients receiving hydroxyurea and those who were not, crizanlizumab may be safely administered as monotherapy or in combination.[14] Crizanlizumab can be used regardless of SCD subtype, as all groups demonstrated benefit from crizanlizumab.[14]

The wholesale acquisition cost per vial of crizanlizumab is $2357, and most patients will require 3 to 4 vials per month ($7071 to $9428).[22] The manufacturer of crizanlizumab, Novartis, has created a program to assist with insurance coverage and case management.[23] In 2020, the Institute for Clinical and Economic Review (ICER) released a report assessing the cost effectiveness of crizanlizumab as well as other agents for SCD.[24] Based on available data, ICER recommends that the price be lowered so that cost of crizanlizumab is aligned with clinical benefit.[24] ICER made the same recommendation for a price reduction of L-glutamine and voxelotor as well.[24] According to the ICER report, crizanlizumab was found to be the most cost-effective in patients with a high frequency (10 per year) of VOCs.[24]

Conclusion

Crizanlizumab appears to be efficacious in lowering the frequency of VOCs in patients with SCD. As a monthly infusion, patient care will require coordination to ensure compliance, and administration may be more challenging in patients with IV access difficulties.[25] It is currently only approved for use in patients who are 16 years of age or older.[12] It remains to be seen if it can be used in pediatric patients with SCD and if it can be combined with other novel agents such as voxelotor. Crizanlizumab shows promise as a preventative agent for VOCs, which may significantly affect the quality of life in patients with SCD.

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