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Short Communication

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Real-World Data of Crizanlizumab in Sickle Cell Disease: A Single-Center Analysis

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Abstract

Background: Crizanlizumab was approved by the United States Food and Drug Administration agency in 2019 for decreasing vaso-occlusive events (VOEs) in sickle cell disease (SCD). Data regarding the use of crizanlizumab in the real-world setting are limited. Our goal was to identify patterns of crizanlizumab prescriptions in our SCD program and evaluate the benefits and identify barriers to its use in our SCD clinic.

Methods: We conducted a retrospective analysis of patients who received crizanlizumab at our institution between July 2020 and January 2022. We compared acute care usage patterns before and after initiation of crizanlizumab, adherence to treatment, discontinuation and reasons for discontinuation. High utilizers of hospital-based services were defined as those with more than one visit to the emergency department (ED) per month or more than three visits to the day infusion program per month.

Results: Fifteen patients received at least one dose of crizanlizumab 5 mg/kg of actual body weight during the study period. The average number of acute care visits decreased following crizanlizumab initiation but was not statistically significant (20 visits vs. 10 visits, P = 0.07). Among high users of hospital-based services, the average number of acute care visits decreased after initiation of crizanlizumab (40 vs. 16, P = 0.005). Only five patients included in this study remained on crizanlizumab 6 months after initiation.

Conclusion: Our study suggests that crizanlizumab use may be helpful in decreasing acute care visits in SCD, particularly among high utilizers of hospital-based acute care services. However, the discontinuation rate in our cohort was extremely high, and further evaluation of efficacy and causes contributing to discontinuation in larger cohorts is warranted.

Keywords: Sickle cell disease; Crizanlizumab; Real-world data

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Introduction

Sickle cell disease (SCD) is characterized by episodes of painful vaso-occlusive events (VOEs) [1] resulting in increased hospital utilization and decreased quality of life [2, 3]. Crizanlizumab is a monoclonal antibody that binds to P-selectin, blocking its interaction with P-selectin glycoprotein ligand (PSGL-1) [4], and has been approved by the United States Food and Drug Administration agency for decreasing SCD VOEs in patients 16 years and older; however, data regarding its use in the real-world setting are limited [5]. While there is growing clinical experience with using crizanlizumab in SCD, published data regarding use of crizanlizumab outside of the clinical trial setting are limited. In addition, experience with crizanlizumab in patients with > 10 acute care visits for VOEs is not widely published. Our goal was to identify patterns of crizanlizumab prescriptions in our SCD program and evaluate the benefits and identify barriers to its use in our SCD clinic.

Materials and Methods

We conducted a single-center, retrospective study evaluating the impact of initiating crizanlizumab in adults (> 16 years) with SCD, seen at the University of California San Diego Health from July 25, 2020 to January 24, 2022. We included patients who had received at least three doses of crizanlizumab of 5 mg/kg of actual body weight and had transitioned to a maintenance dosing regimen. Dosing guidelines were followed per FDA label [6].

We collected data from the electronic medical records including age, sex, weight, date of crizanlizumab initiation, date of acute care visit, visit setting, concomitant use of other SCD medications, date of discontinuation (if applicable) and reason for discontinuation (if applicable). Retrospective data collection and review was approved by University of California San Diego Human Research Protection Program (IRB: #210705).

Table 1. Analysis of Acute Care Visits Before and After Crizanlizumab Initiation

Subject ID	SCD genotype	Pre-crizanlizumab acute visits	Post-crizanlizumab acute visits	Doses received	Concomitant SCD medications	Reason for discontinuation of crizanlizumab
1	Hb SS	57	25	6	L-glutamine	Unable to keep appointments
2	Hb S/β0	59	33	6	None	Unable to keep appointments
3	Hb SS	17	0	4	Voxelotor	Transportation issues
4	Hb S/β0	27	7	4	None	Unable to keep appointments
5	Hb SS	9	9	7	L-glutamine	Perceived lack of efficacy
6	Hb SS	0	0	5	Hydroxyurea	Unable to keep appointments
7	Hb SC	0	0	7	None	Continues on med
8	Hb SS	0	4	9	Voxelotor	More pain
9	Hb SS	12	16	6	Hydroxyurea	Unable to keep appointments

SCD: sickle cell disease.

The study conformed to all ethical principles outlined by the Declaration of Helsinki. We collected data pertaining to acute episodes of pain with no medically determined cause other than a VOE that resulted in a visit to the emergency department (ED) or an outpatient infusion center (IC) for management. We collected the number of acute care visits for 6 months before, and 6 months after the initiation of crizanlizumab. We classified patients as "high utilizers" if they presented to the ED one or more times a month, or to the IC more than three times a month. We used paired *t*-test to compare acute care use before and after crizanlizumab. Statistical analysis was performed using Graphpad Prism version 9.

Results

Fifteen patients received at least one dose of crizanlizumab during the study period, and nine met the inclusion criterion of having received at least three doses per dosing guidelines. Excluded patients consisted of three patients who received only one dose of crizanlizumab and three patients who did not receive more than two consecutive doses. Of the nine patients that met inclusion criteria, eight had severe SCD genotypes (Hb SS = 6, HbS/β0 thal = 2) and one patient had a mild-moderate genotype (Hb SC). Majority of patients were female (5, 55.6%) and the median age was 30 years old. The average number of acute visits decreased following crizanlizumab initiation but was not statistically significant (20 visits vs. 10 visits, P = 0.07). The majority of the acute care visits occurred at the IC, for management of acute pain (152 total visits before crizanlizumab vs. 76 visits after initiation of crizanlizumab). Further analysis of each patient and respective number of VOEs is shown in Table 1. We then looked at usage of hospital-based services and four patients met the criteria for high utilizers. The average number of acute care visits decreased after initiation of crizanlizumab in the high utilizers (40 vs. 16, P = 0.005). Only five of the nine patients included in this study remained on crizanlizumab 6 months after initiation, and only one person remains on treatment now. Reasons for discontinuation of crizanlizumab include difficulty accessing care including lack of transportation (2), inability to adhere to scheduled appointments (4), perceived lack of efficacy (1) or increased pain (1).

Discussion

Acute care utilization for management of pain associated with VOEs remains a challenge for individuals with SCD [2]. A pivotal trial by Ataga et al showed a reduction in the median rate of SCD VOE per year from 2.98 (placebo) to 1.63 upon treatment with crizanlizumab [4], and this led to the approval of this medication for treatment of SCD. However, there are limited data on the real-world use of crizanlizumab; particularly as it applies to patient selection for initiating this therapy, challenges in administering the medication and adherence to treatment.

We start patients on crizanlizumab therapy with the goal of decreasing VOEs. In general, our strategy has been to offer crizanlizumab for patients who report more than two VOEs a year, based on the inclusion criteria for the SUSTAIN trial [4]. However, in contrast to the trial which only included VOEs requiring a visit to a specific medical facility or health care professional, we consider both VOEs that are managed at home and/or in the hospital to make this recommendation, as most of our adult patients manage their VOEs at home. Our approach is based on previously published data [7] which show that patients with SCD most commonly manage even severe pain without an outpatient, ED or hospital visit, but would greatly benefit from a disease modifying strategy that decreases their pain. Of the nine patients who were included in this study, only two patients were concomitantly on hydroxyurea. Among the remaining patients, one individual had Hb SC subtype with infrequent VOE (reported 4 - 5 episodes per year, mostly managed at home) and was not on hydroxyurea. The remaining six patients were prescribed hydroxyurea previously but discontinued it because of difficulty in complying with oral medication (n = 2) or because of unacceptable side effects (n = 4) including nausea, abdominal discomfort, hair loss, and nail pigmentation. Hematologic toxicity was not the reason for discontinuation of hydroxyurea in any of the patients in this study.

In our cohort, crizanlizumab therapy decreased acute care utilization for VOE management, particularly among high utilizers of acute hospital-based services. However, the number of acute care visits was much higher in our cohort, when compared to Ataga's study. One explanation for this observation is that the trial only included individuals with 2 - 10 VOEs in the preceding 12 months and clinical trial participants may not be entirely representative of the SCD population in the real-world setting. Also, in our cohort, most acute care visits occurred in the outpatient setting and at the IC. An average SCD VOE can take 7 - 10 days to resolve, and this may require multiple IC visits per VOE episode. It is also possible that some of the IC visits were for management of chronic pain exacerbation, rather than an acute VOE; however, we were not able to distinguish between the two in this cohort. In individuals with SCD and high burden of disease, chronic pain can be difficult to separate from acute pain; however, it can significantly contribute to SCD morbidity and poor quality of life [8]. Based on our data, crizanlizumab treatment may have a positive impact on limiting exacerbations of chronic pain, particularly amongst high utilizers, and this merits further study.

Another striking and remarkable aspect of our study is the high discontinuation rate. While we offered crizanlizumab to all eligible patients with SCD, only 15 chose to start therapy and of those, only nine patients went on to receive maintenance dosing and only one patient remained on medication at the end of the study period. We see patients once a month in our outpatient sickle cell clinic if prescribing narcotics for pain management, and less frequently (typically every 3 - 4 months) otherwise. Patients are provided verbal and written communication regarding all their upcoming appointments at every clinic visit. In addition, patients also receive reminder notifications by phone or text message (based on their choice) for infusion appointment (for crizanlizumab). All the patients reported in this study understood that this was an intravenous medication and that it required monthly visits. None of the patients started any other chronic therapies during this period. To our knowledge, insurance issues were not a barrier for the patients presented in this cohort. Insurance barriers are typically encountered at the start of therapy (by our prior authorization team), while in this study, we only present patients who were able to get at least three doses of the medication, had continued access to the medication, and where cost was not a barrier to continued treatment.

Despite accounting for these factors, patients face several barriers in accessing care for SCD [9]. As seen in our cohort, most patients did not continue treatment, due to difficulty in adhering to appointments. Five patients discontinued crizanlizumab because they were unable to keep their appointments. Of these, four patients (subject no. 1, 2, 4, 9) were not compliant with their preventative care appointments or their medications, and instead relied on acute care utilization for pain management as the primary strategy to manage their SCD, and subsequently missed their scheduled appointments for crizanlizumab multiple times. Subject 6 expressed difficulty in maintaining monthly appointments because of other socioeconomic factors and decided to stop the treatment. Subject 3 had difficulties with transportation and elected to discontinue therapy for that reason. Neurocognitive issues, social determinants of health, lack of transportation and poor health literacy can pose significant challenges in accessing care in SCD and need to be taken into consideration while managing SCD and prescribing therapies. Subject 5 discontinued treatment since they did not think it was effective or making any change in their health. Subject 8 reported worsening pain in their lower back and legs and worsening of chronic pain for a few days after receiving crizanlizumab, following which their pain returned to baseline levels, and chose to discontinue crizanlizumab. Low back pain and arthralgia have been reported as a potential adverse effect of crizanlizumab therapy in the SUSTAIN trial [4]. To our knowledge, none of our patients experienced any serious adverse events and none of our patients discontinued crizanlizumab over safety concerns.

The major limitations of our study include the small sample size and retrospective nature of the analysis. Since this study was based on chart review, we could not reliably collect data pertaining to VOE managed at home and hence we only evaluated data related to acute care utilization. However, we believe that despite the small sample size, this study provides valuable insights regarding challenges involved in caring for individuals with SCD.

Conclusions

In summary, our study suggests that crizanlizumab use may be helpful in decreasing acute care visits in SCD, particularly among high utilizers of hospital-based services. However, the discontinuation rate in our cohort was extremely high, and further evaluation of efficacy and causes contributing to discontinuation in larger cohorts is warranted.

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None to declare.

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Conflict of Interest

None to declare.

Informed Consent

Informed consent was not deemed to be necessary by the IRB and the requirement was waived.

Author Contributions

All authors have contributed to the study design, data interpretation, draft and approved the submitted version. HC performed the research, collected and analyzed the data and wrote the first draft. SB, JG, SS, and ALN reviewed the data critically and edited the manuscript. SG designed the study, analyzed the data and wrote the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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