Outcomes and Barriers to Use of Novel Sickle Cell Therapeutic Agents in a Community Health Center

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Abstract: Sickle cell disease is genetic red blood cell disorder transmitted via an autosomal recessive mutation due to valine replacing glutamicacid on the beta globulin chain of the hemoglobin molecule. The disease impacts millions of people worldwide majority living in sub-Saharan Africa and India and impacts approximately 100,000 Americans mostly those of African descent. [2-3] In 2019, two novel treatment agents for sickle cell anemia, crizanlizumab (Adakveo) and voxelotor (Oxbryta) were approved by the United States Food and Drug Administration (US FDA) [7, 8]. Both medications offer sickle cell patients improved control of their disease by reducing sickling of the red blood cells (voxelotor) and the painful effects of vaso-occlusive crises, (crizanlizumab). We studied the effects of crizanlizumab and voxelotor on a population of patients in a sickle cell clinic. Fifty-two charts were reviewed for inclusion in the study; 12 patients were using crizanlizumab and 12 patients were using voxelotor. Eight patients met criteria for evaluation of crizanlizumab and 7 patients for voxelotor. Of all data collected, the only significant difference between baseline measures and post-therapy measures was for voxelotor and hemoglobin levels at baseline and at 3 or more months post therapy. This was a small study which reflects the experience of one clinic; sickle cell providers must continue to address the social determinants of health, psychosocial and psychological needs of their patients in addition to prescribing these novel medications.

Keywords: Medication adherence, Community Health Center, Crizanlizumab, SDoH, Sickle cell, Voxelotor.

INTRODUCTION

Sickle cell anemia is genetic red blood cell disorder transmitted via an autosomal recessive mutation due to valine replacing glutamicacid on the beta globulin chain of the hemoglobin molecule [1]. The disease impacts millions of people worldwide, majority living in sub-Saharan Africa and India, and approximately 100,000 Americans, mostly of African descent [2-3]. Currently the only cure for sickle cell disease is bone marrow transplant, which is a high-risk procedure with significant potential for complications or failure [4, 5]. The natural history of this disease results in early mortality and significant lifetime morbidity and suffering due to multi system damage and severe pain during the classic vaso-occlusivecrises (VOC). Historically, there has been very little research and drug development for the treatment of sickle cell disease, qualifying drugs developed for this condition to be approved as orphan products by the United States Food and Drug Administration (US FDA) [6]. Hydroxyurea was approved for treatment of adults with sickle cell disease in 1998 and in 2017 for use in children [7]. L- Glutamine (Endari) was the next new drug approved in 2017 [8]. In 2019, two novel treatment agents for sickle cell anemia, crizanlizumab (Adakveo) and voxelotor (Oxbryta) were also FDA approved [9, 10]. Both medications offer sickle cell patients improved control of their disease by reducing sickling of the red blood cells (voxelotor), and the painful effects ofvaso-occlusive crises (crizanlizumab).

Crizanlizumab, administered intravenously at week 0, 2 and then every 4 weeks, is a humanized monoclonal antibody. It blocks P-selectin, a key adhesion mediator in the inflammatory process that occurs at the vascular endothelial level occurring during a VOC. Inflammatory cells including the sickle erythrocytes, monocytes, neutrophils and platelets result in the occlusion of the blood vessel causing pain. Blockage of P-select in by crizanlizumab reduced the frequency and duration of vaso-occlusivecrises in addition to reduced hospitalizations and duration of admissions [11].

Voxelotor is a hemoglobin-S (Hb S) polymerization inhibitor that reversibly binds to hemoglobin to stabilize the oxygenated hemoglobin state and has been shown

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E-ISSN: 2312-5411/21

to significantly increase hemoglobin levels and reduce markers of hemolysis [12]. Both these medications have the potential to modify the natural history of sickle cell disease with effects seen within a few months of initiation of treatment.

We studied the effects of crizanlizumab and voxelotor on a population of patients in a sickle cell clinic at Five Rivers Health Centers, a Federally Qualified Health Center (FQHC) located in Dayton, Ohio a relatively diverse city with 37.9% of its population identifying as African American or Black [13]. FQHCs typically provide care to medically underserved populations. In 2020, 67% of patients served by Five Rivers were insured through Medicaid. The Five Rivers sickle cell clinic was established in 2014 to address the need to provide a medical home for adult sickle cell patients in the Dayton community. The clinic currently serves 52 adult patients and collaborates with the local children's hospital, Dayton Children's to transition pediatric patients to adult care. The clinic is staffed by an internal medicine physician, a clinical pharmacist, nurse and an integrated behavioral health provider. Hematology-oncology fellows and internal medicine residents from the Wright State University Boonshoft School of Medicine rotate through the clinic several months a year.

Sickle cell patients seen in the clinic for at least 12 months and prescribed either crizanlizumab or voxelotor for at least 6 months were eligible for this study. We evaluated the number of emergency department visits and hospital admissions in patients on crizanlizumab, and the number of red blood transfusions, hemolysis markers including bilirubin and reticulocyte counts and change in hemoglobin levels in patients on voxelotor. We compared data in eligible patients 6 months prior to initiation of the therapies to the same data points 6 months post initiation.

METHODS

This study involves human subjects and was approved by the University of Cincinnati Institutional Review Board on October 21, 2020. Chart reviews of all 52 patients were performed to determine eligibility and to collect clinical data (Table **1**). Patients eligible for this study include those who receive care for sickle cell anemia at Five Rivers Health Centers and received either voxelotor or crizanlizumab for at least 3 consecutive months after January 1, 2020, and through February 28, 2021. Patients treated with voxelotor or crizanlizumab by a hematologist or other provider outside of Five Rivers were excluded due to lack of complete data. Patients with documented poor adherence to either medication were excluded from data analysis but are included as a part of the discussion section below.

Data collected included age and sex of patients, treatment (voxelotor or crizanlizumab), date of initial therapy, and concurrent use of hydroxyurea and/or deferasirox. Data collected for patients treated with voxelotor includes the most recent hemoglobin prior to date of initiation and hemoglobin three or more months after therapy started, LDH at baseline and 3+ months, reticulocyte count at baseline and 3+ months, indirect bilirubin at baseline and 3+ months and number of blood transfusions 6 months prior to therapy and 6 months following therapy. For patients treated with crizanlizumab, data collected included the number of emergency department (ED) visits and hospital admissions due to vaso-occlusive crises 6 months prior to therapy initiation and 6 months after therapy.

Statistical Analysis: Data was recorded on Microsoft Excel. A paired T-test was used to compare baseline data to post-treatment data.

RESULTS

Table 1: Baseline Characteristics

Total Number of Patients	52
Gender	44.23% male (n=23) 55.77% female(n=29)
Race	Black/AA98.08% (n=51) White (middle Eastern) 1.9% (n=1)
Percentage with one or more social determinants of health triggers	84.62% (n=44)
Percentage on hydroxyurea	82.69% (n=43)
Percentage on hydroxyurea plus another disease modifying (including L-glutamine)	65.38% (n=34)

Fifty-two (52) charts were reviewed to determine eligibility (Figure **1**). Twelve (12) patients were initiated on crizanlizumab; 2 discontinued after only 2 infusions due to adverse reactions. 10 patients (19.2%) received crizanlizumab for the full study period however 3 were excluded due to receiving this medication via an outside provider. Seven (7) patients (13.5%) were included in analysis, 3 male and 4 female. Twelve (12)

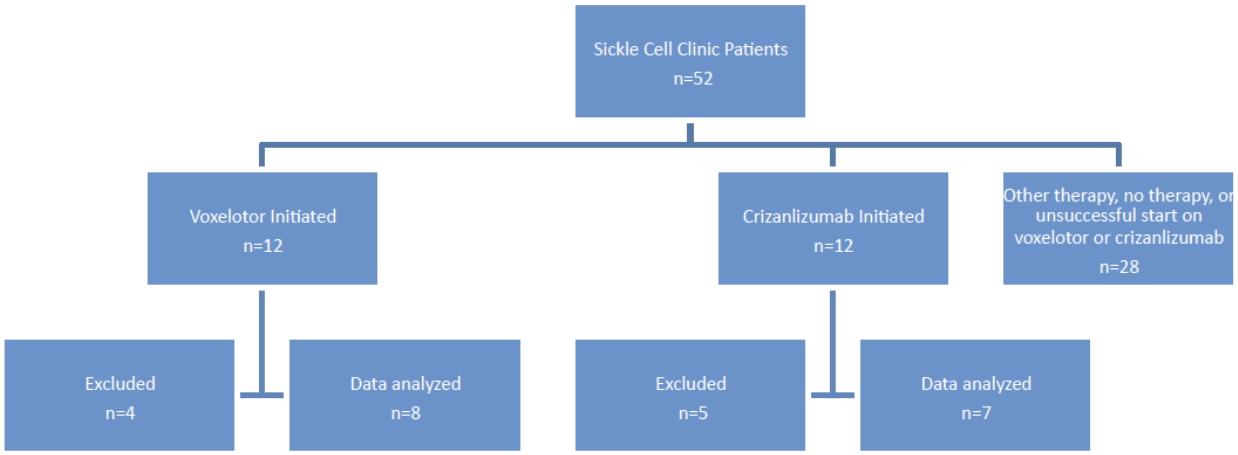

Figure 1: Study Inclusion.

patients were initiated on voxelotor, however 4 discontinued due to adverse reactions. Eight (8) patients (15.4%) were included in the analysis, 4 male and 4 female.

For crizanlizumab, there was no difference in number of admissions for VOC to either the ED or full hospital admission in the six months before and six months after initiation. Of the 8 patients analyzed on crizanlizumab, only 3 followed the exact dosage schedule recommended by the manufacturer, receiving doses at week 0, 2 and every 4 weeks afterwards. The other 5 missed doses and then resumed for various reasons.

For voxelotor, there was no difference noted in LDH, indirect bilirubin, or reticulocyte count. Of note, there was not complete or accurate data for all patients with these lab measures. However, there was a statistically significant difference in hemoglobin from a baseline average of 8.28 mg/dl to an average of 9.65 mg/dl (p=0.026) after 3-6 months of voxelotor therapy. Despite this change in hemoglobin, there was no significant difference between number of blood transfusions 6 months prior to voxelotor initiation and 6 months following.

DISCUSSION

This was a small study yet still reflects the challenges of medication usage and adherence in a community health center patient population. Many of our patients are still being denied coverage of these medications by their health insurers contributing to the low numbers on crizanlizumab and voxelotor. Our results did not show a significant reduction in admissions or ED utilization in patients on crizanlizumab, nor did it show a reduction in hemolysis markers or number of blood transfusions in patients on voxelotor. There was a statistically significant increase in the hemoglobin levels in patients on voxelotor. This study is a real-world example of one small clinic's experience with two of the new therapies for sickle cell anemia. We did not have a large population of patients with which to measure differences in therapy. Additionally, the 6-monthfollow up may have been too early to show significant improvement. We did not exclude patients who did not stay on schedule with crizanlizumab infusions or missed voxelotor doses.

Sickle cell is associated with physical disability, cognitive impairment and psychological disorders including depression and anxiety [14-16]. As a result, a significant percentage of patients are unable to maintain employment and are on Medicaid, the government insurance program and face several social determinants of health (SDoH) factors [17]. We postulate that as a result, our patient population which is primarily Medicaid have multiple barriers which played a significant role in patient adherence, negatively impacting our results.

In addition to the a fore mentioned challenges, there are additional systemic barriers that impede patient adherence. The prior authorization process and delivery of these medications may prove challenging to patients in general and more so in a Medicaid eligible patient. Voxelotor patients must respond to multiple phone calls or emails for initial approval and must also respond to monthly phone calls before home deliveries are scheduled. Some patients may not have phone minutes, or do not pick up the phone due to work or

other restrictions. The inability to use local pharmacies to dispense voxelotor presents a challenge especially in those with housing insecurity. Despite our clinic scheduling the initial 4-6 appointments for crizanlizumab infusions once approved, patients miss appointments due to forgetfulness, transportation issues, lack of childcare, inability to leave work, losing pay, hospital admissions to name a few. Home IV infusions of crizanlizumab should be considered for approval in challenging situations. Due to having a chronic unpredictable disease, depression is common in sickle cell patients further impacting medication adherence [18]. Depending on the level of social support and resources available, patients will not get the full benefit of these critical medications even when approved for their use. These factors highlight the need to go beyond prescribing medications and provide support between visits using a community health workers or other clinical staff including behavioral health.

We agree that availability of these medication is a progress, however as we offer them to patients, their real-world challenges need to be addressed in a programmatic manner. The next steps for our clinic are to delve into patient barriers and formulate individual implementation plans. Our clinic currently does not have a sickle cell community health worker, but we plan to use grant dollars to hire for this position to help address some of these needs, link patients to appropriate services and act as a liaison between patients and clinical staff in between appointments.

CONCLUSION

The excitement about having more than one medication for the treatment of sickle cell disease remains palpable. Sickle cell patients may be able to modify the natural history of their disease and potentially live longer, healthier lives with less complications and organ damage. Patients prescribed these medications may need additional support to overcome barriers to obtaining and staying on their medications to achieve full benefit. Sickle cell providers must continue to address the SDoH, psychosocial and psychological needs of their patients in addition to prescribing these novel medications.

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Received on 15-05-21 Accepted on 25-06-21 Published on 17-07-2021

DOI: http://dx.doi.org/10.12974/2312-5411.2021.08.1