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Patient perception of voxelotor treatment benefit in sickle cell disease

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ABSTRACT

Patients with sickle cell disease (SCD) experience a range of clinical symptoms, including acute and chronic pain, fatigue, and respiratory problems, as well as chronic organ complications that can lead to disability and accelerated mortality. Voxelotor is a first-in-class therapy that targets sickle hemoglobin polymerization, the root cause of SCD. It is approved by the US Food and Drug Administration for treatment of SCD in patients aged 4 years and older and in the European Union and United Arab Emirates for the treatment of SCD in patients aged 12 years and older. Here, we report the single-center experience of both clinician-determined and patient-reported benefits of voxelotor in 27 consecutive patients treated for at least 8 weeks. Clinical Global Impression of Change and Patient Global Impression of Change rating scales were used to capture clinicians' and patients' perceptions of change in overall patient health-related quality-of-life with voxelotor treatment. Laboratory data were also collected to assess clinical response to treatment. As observed in previous clinical studies, hemoglobin concentrations and markers of hemolysis were improved in patients treated with voxelotor. Most patients reported marked improvement in disease symptoms, which correlated well with the clinicians' assessments. Although limited by the retrospective open-label study design, these findings suggest that voxelotor use has a positive impact on outcomes in patients with SCD.

INTRODUCTION

Sickle cell disease (SCD) is a complex, lifelong disease that affects millions of people worldwide.[1 2] Clinical manifestations of SCD can vary considerably in time of onset, frequency, and severity, and can affect multiple systems.[1–3] Disease-related symptoms and complications adversely affect the physical and social functioning, general health, and emotional well-being of patients and contribute to reduced health-related quality of life (QOL).[4–7] Therefore, in addition to measuring treatment-related physiological and symptomatic effects, it is important to assess whether clinical benefits translate to more holistic improvements in a patient's health status.

Voxelotor is a novel sickle hemoglobin (HbS) polymerization inhibitor that has been shown to improve key measures of red blood cell (RBC) heath in patients with SCD.[8–10] In a phase III clinical trial, patients receiving voxelotor therapy showed rapid and durable improvements in hemoglobin (Hb) concentrations and markers of hemolysis.[11 12] In the same study, clinicians rated the impact of voxelotor on patient disease status using the Clinical Global Impression of Change (CGI-C),[12] a validated assessment of the clinician's view of a patient's global functioning before and after initiating a study medication.[13] Voxelotor-treated patients were rated as having an improved health-related QOL at week 72, with trends of improvement observed as early as week 24.[12] Although not captured in the study, patient impressions of their overall health status are equally valuable and important to consider. This real-world analysis compares patient and clinician assessments of change in symptoms or clinical status in response to voxelotor treatment. Our findings suggest that treatment with voxelotor is associated with increased benefit in patient functioning.

MATERIALS AND METHODS

Real-world clinical data were collected retrospectively from 27 consecutive voxelotor-treated patients with SCD at The University of Texas Comprehensive Sickle Cell Center; only patients with at least 8 weeks of data collection were included. In order to be included in this retrospective analysis, patients must have been treated with voxelotor and had (1) increased steady-state hemolysis, as evidenced by increased indirect bilirubin of >3 mg/dL, lactate dehydrogenase >300 U/L, and Hb <8.5 g/dL; (2) extensive alloimmunization that put them at risk of a transfusion reaction, as to avoid complications from future blood transfusions; and (3) organ dysfunction that was expected to be improved by the mechanism of action of voxelotor (ie, improved oxygenation, increased Hb). Examples of such organ dysfunction include chronic hypoxia, pulmonary hypertension, cerebrovascular dysfunction, or multiple organ dysfunction.

Daily oral voxelotor 1500 mg was added to existing SCD treatment regimens, which in some cases included hydroxyurea. Analyses included the comparison of Hb levels and reticulocyte percentages before and after initiation of voxelotor treatment, as well as the evaluation of overall patient disease status using the

CGI-C and Patient Global Impression of Change (PGI-C) scales. The CGI-C is a single-item, 7-point graded scale that captures a clinician's summary rating for a patient's overall health status, taking into consideration multiple symptom domains and all available and clinically relevant patient information, including history, illness severity, and functional ability.[13] This simple instrument is widely used in US Food and Drug Administration–regulated trials and correlates well with standard, well-known research drug efficacy scales.[13] Patients' laboratory and clinical data were reviewed by two experienced hematology providers from the Sickle Cell Center in order to determine the CGI-C rating. One of the providers was the primary hematologist, and the rating the two providers agreed on was used here. The PGI-C is the patient-reported outcome counterpart to the CGI-C, reflecting a patient's impression of improvements with treatment intervention.[14] The protocol was amended to allow assessment of PGI-C data. Ratings on both scales are rated as 'very much improved', 'much improved', 'minimally improved', 'no change', 'worse', 'much worse', or 'very much worse' since treatment initiation. Data collection was performed in accordance with the The University of Texas Health Science Center at Houston Standing Data Collection Protocol that permits the documentation and publication of anonymized patient data collected for standard clinical care. In an effort to reduce bias, PGI-C ratings collected by the study staff were withheld from clinicians until the clinicians completed the CGI-C assessments.

RESULTS

Of the 27 patients, 4 did not have complete laboratory and PGI-C data. One patient discontinued voxelotor due to pregnancy and was excluded from the analysis. Analysis was performed on data from 23 patients for whom information on Hb levels, reticulocyte percentages, CGI-C, and PGI-C was available. Seventeen of the patients had complete laboratory data, and 23 patients provided PGI-C information. Of note, laboratory test frequency was limited by COVID-19 pandemic restrictions.

Data were analyzed from 23 patients, who ranged in age from 20 to 66 years; 65% were female. Most patients (91%) had the SCD genotype HbSS, and the remaining 9% had HbSβ^0; no patient had HbSβ^+ or HbSC genotypes. Six patients were receiving hydroxyurea at baseline. The impact of voxelotor on key laboratory parameters was assessed ≥2 weeks after initiating voxelotor (n=17 patients with complete laboratory data). The mean (SD) change in Hb concentration from baseline was 1.14 g/dL (1.38 g/dL). A waterfall plot for the change in Hb from baseline for individual patients is shown in figure 1A. Observed Hb improvements were comparable to those seen in the HOPE trial.[15] Reductions in markers of hemolysis, as measured by mean change from baseline, were observed for reticulocyte percentage (–4.2%, SD=4.11%; figure 1B) and total bilirubin (–1.01 mg/dL, SD=0.98 mg/dL; figure 1C). One patient showed reduced RBC sickling and was less anemic 21 days after initiating treatment with voxelotor.

Each patient provided an assessment of improvement with voxelotor treatment using the PGI-C. A total of 70% (16 of 23) of patients described their overall health as 'very much improved' or 'much improved', 22% (5 of 23) described their clinical status as being 'minimally improved', and 8% (2 of 23) perceived 'no change' after initiation of voxelotor (figure 2A). Some patients also noted substantial improvement in energy and less pain at their typical sites of chronic pain while on voxelotor. The healthcare provider assessed each patient for improvement in health status with voxelotor treatment using the CGI-C. Clinicians provided similar rankings for the patients being analyzed: 83% (19 of 23) of patients were rated as 'very much improved' or 'much improved', 13% (3 of 23) were rated as 'minimally improved', and 4% (1 of 23) were rated as having

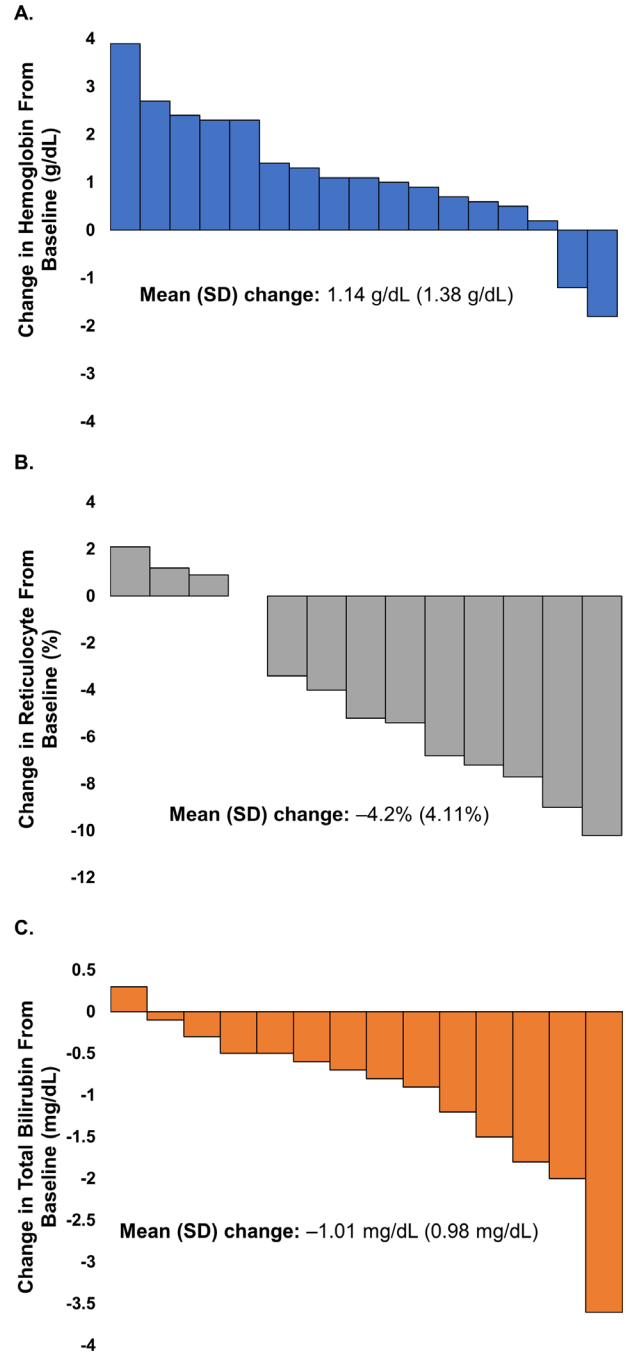

Figure 1 (A) Change in hemoglobin level from baseline. (B) Change in reticulocyte percentage from baseline. (C) Change in total bilirubin from baseline.

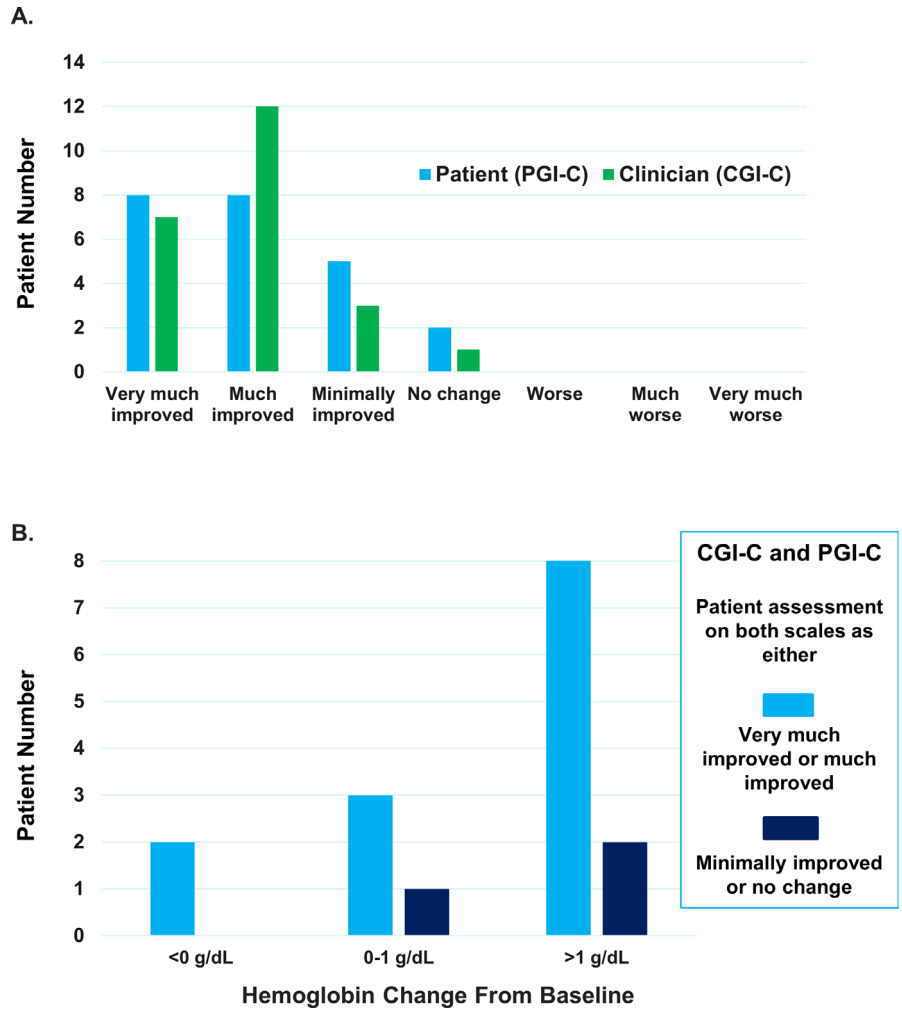

Figure 2 (A) Patient and clinical assessment improvement with voxelotor therapy. (B) Hemoglobin change and clinical improvement. CGI-C, Clinical Global Impression of Change; PGI-C, Patient Global Impression of Change.

undergone 'no change' in response to voxelotor treatment. CGI-C and PGI-C outcomes were further stratified by Hb response, which suggested that clinical improvement (ratings of 'very much improved' or 'much improved') was not limited to patients who had increases in Hb greater than 1 g/dL (figure 2B). For some patients who reported substantial clinical improvement ('very much improved' or 'much improved' symptoms), Hb levels had declined or improved only slightly from baseline.

About 30% of the patients reported mild to moderate diarrhea. This issue was managed by reduction in voxelotor dose until diarrhea improved, at which point patients were titrated back to the recommended dose. For more severe diarrhea, voxelotor was interrupted for 2–3 days and then restarted at a lower dose, with or without the addition of antidiarrheal medications. All patients were alerted to the possibility of diarrhea at voxelotor initiation and were advised not to stop treatment without contacting the physician for guidance on management. Three patients experienced mild headache that resolved within 2 months, and one patient reported arthritic pain in the hands.

DISCUSSION

This is a real-world study using both PGI-C and CGI-C scales to assess SCD improvement after initiation of voxelotor treatment. In this analysis, most patients reported considerable overall improvement in their health status, which correlated well with the clinicians' impressions. Additionally, some patients indicated substantial improvements in their energy levels and reductions in pain at their typical sites of chronic pain while on voxelotor. One patient noted resolved chronic lower back pain and improved energy after 2 weeks of voxelotor therapy. This patient was consequently able to engage in full-time work and described feeling 'like a normal person'. Another patient reported being more energetic and noticed improvements in their self-esteem and mental health after starting voxelotor. After treatment, this patient was able to work full-time, started attending school part-time, and considered their major depressive disorder to be resolved. Anecdotal evidence of improvements in oxygen saturation, hospitalization rates, and intensity and duration of vaso-occlusive crisis–related pain was also gathered.

Notably, patient-reported and clinician-determined health-related QOL improvements were not limited to patients who had an increase in Hb greater than 1 g/dL. Clinical improvements were observed even for patients whose Hb declined or improved marginally. Current patient-reported outcome assessments in SCD tend to focus on capturing domain-specific symptoms and impacts such as pain, depression, and fatigue.[16] However, there is a need to incorporate tools that collectively evaluate the broader symptomology and complications of SCD to determine the comprehensive status of a patient's treatment progress. The PGI-C and CGI-C are easy-to-interpret assessments that can be used effectively to track a patient's integrative experience while receiving SCD therapy.[13 14] Experienced clinicians who are familiar with the variability in clinical presentation and patterns of SCD can use the CGI-C to chronologically record changes to a patient's disease status at different time points after the adoption of a treatment regimen.[12]

It should be noted that this study has several limitations. Retrospective data were limited (eg, we had no record of patients who were denied coverage by insurance), which may limit our patient population. Because this study was unblinded, all patients were aware they were receiving voxelotor; thus, clinical improvements in the treatment group may represent an expectancy in patients rather than a pharmacologic effect. In addition, limited qualitative information was collected from patients and clinicians on the reasoning behind the PGI-C and CGI-C ratings. A clear correlation between global impression of change and change in Hb, therefore, is difficult to interpret.

As observed in the HOPE trial, patients analyzed in this study showed improvements in Hb levels and markers of hemolysis. Due to the implementation of COVID-19 restrictions at the time of data collection, most patients were unable to have laboratory assessments at the desired frequency, thus resulting in limited data. No new safety signals were detected throughout the duration of the study. Approximately 30% of patients reported mild to moderate diarrhea, which was managed by dose reduction of voxelotor, followed by retitration to a higher dose with or without concurrent antidiarrheal medications. In summary, this study suggests that most patients with SCD perceived a benefit with voxelotor therapy in terms of improvement in their condition and level of functioning. Moreover, these findings correlate with the clinical impressions of healthcare providers.

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Patient consent for publication Not applicable.

Ethics approval All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committees, and with the 1964 Declaration of Helsinki and its later amendments, as revised in 2013. Approval was obtained from the Committee for the Protection of Human Subjects at The University of Texas Health Science Center at Houston, reference number HSC-MS-20-0768. Formal consent is not required for this type of study.

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