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A retrospective research of adverse event reporting system events for voxelotor based on the FAERS database

Ying Lin[1], Hua Li[1], Yuqing Dong[1], Weiyue Fang[1], He Huang[1], Muqing He[1], Xiaohai Zhou[1] and Ni Sun[1*]

Abstract

Background Sickle cell disease (SCD) is a severe genetic disorder causing anemia, pain, and organ damage, affecting millions globally. Voxelotor, approved in the United States in 2019, targeted sickle cell disease pathophysiology. Despite its therapeutic benefits, concerns remain regarding its long-term safety and potential side effects, including headaches and gastrointestinal disturbances. This study used the FDA Adverse Event Reporting System (FAERS) to assess voxelotor's safety, aiming to enhance treatment strategies and clinical decision-making in SCD management.

Methods In this study, we utilized the FAERS to extract voxelotor-related adverse event reports from 2019 to 2024. We conducted descriptive and disproportionality analyses using four algorithms: Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Multi-item Gamma Poisson Shrinkage (MGPS) to identify significant adverse event signals. The reliability of voxelotor adverse drug reactions (ADRs) was further improved by comparing with hydroxyurea ADRSs. Finally, adverse reactions were divided into acute ADRS, delayed ADRs and efficacy related reports to analyze the adverse event onset time.

Results A total of 16,677,340 case reports were collected in the FAERS database, of which 20,902 reports related to voxelotor were identified. Voxelotor induced adverse events occurred in 27 system organ categories (SOC). Key system organ classes affected were the blood and gastrointestinal systems. Notably, some adverse events, such as priapism and osteonecrosis, were not listed on the drug's label. The median adverse event onset time of acute ADRs, delayed ADRs and efficacy related reports were 1, 189.5 and 271 days, respectively.

Conclusion This study systematically analyzed ADRs of voxelotor, highlighting the need for ongoing monitoring and further research on voxelotor's long-term safety and efficacy in treating sickle cell disease.

Keywords FAERS database, Voxelotor, Adverse event, Real-world data analysis, Disproportionality analysis

*Correspondence:
Ni Sun
212153@wzhealth.com
[1]Department of Hematopathology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, 1111 Wenzhou Avenue, Wenzhou 325000, China

Introduction

Sickle cell disease (SCD) is a multisystem disorder characterized by chronic hemolytic anemia, severe acute and chronic pain, as well as end-organ damage that occurred across the lifespan, and is one of the most common severe monogenic disorders in the world [1, 2]. It affected approximately 100,000 people in the United States and more than 3 million people worldwide. Acute and chronic pain and end-organ damage occurred throughout the lifespan of people with SCD, contributing to high morbidity, resulting in a median life expectancy of just 43 years in the United States [2]. Over the years, various therapeutic strategies have been developed with the primary objectives of reducing vaso-occlusive episodes, managing pain, and preventing of long-term organ damage [3, 4]. Traditional treatments, such as hydroxyurea, which increased fetal hemoglobin levels [5] and blood transfusions aimed at reducing the concentration of sickle hemoglobin [6], have been widely used. However, these treatments have limitations, including side effects and complications such as iron overload in patients receiving frequent transfusions [7].

Recent advancements in the treatment of SCD have increasingly focused on targeting the underlying pathophysiology to address the root causes such as inducing fetal hemoglobin, reducing anti-sickling or cellular adhesion, and activating pyruvate kinase-R, rather than merely alleviating symptoms [2]. One of the most promising developments in this area is voxelotor, an oral small molecule that inhibits the polymerization of hemoglobin S (HbS). Approved by the FDA in 2019, voxelotor functions by increasing the oxygen affinity of hemoglobin, thus preventing the sickling of red blood cells—a hallmark of SCD pathophysiology [8, 9]. In the HOPE trial, voxelotor treatment resulted in a statistically significant increase in hemoglobin level [10]. A post hoc analysis of the HOPE data also revealed that nearly all patients who received voxelotor experienced clinical improvement in leg ulcers [11, 12]. Despite the promising therapeutic benefits of voxelotor, the long-term safety and adverse effected profile of the drug remain critical areas for ongoing investigation. Although voxelotor was generally well tolerated, it was associated with side effects such as headache, gastrointestinal symptoms, and rash and may increase the risk for venous thromboembolism [13, 14].

Pharmacovigilance, involving the continuous monitoring of a drug' safety after it released to the market, is essential for identifying rare but potentially serious adverse events that may not have been detected during pre-approval clinical trials. The FAERS serves as a key resource for collecting real-world safety data on drugs [15]. This study utilized the FDA Adverse Event Reporting System (FAERS) database to assess the safety profile of voxelotor in SCD patients, with the aim of identifying potential adverse events associated with its use. This study evaluated the safety of voxelotor in patients with SCD using the FAERS database with the goal of identifying potential adverse events associated with the use of voxelotor, which was critical for optimizing treatment strategies and guiding clinical decisions in SCD management.

Materials and methods

Data sources

The FAERS is a publicly accessible database that consolidates voluntary safety reports submitted by healthcare professionals, pharmaceutical manufacturers, consumers, and patients worldwide. It serves as a critical tool for post-marketing surveillance, enabling the detection of potential safety signals associated with drugs and therapeutic products [16]. In our study, we extracted voxelotor-related AE reports submitted between 2019 and 2024 from the FAERS database. In order to improve the reliability of voxelotor-related AEs, we extracted hydroxyurea-related AE reports between 2004 and 2024 to distinguish true AEs rather than symptoms of disease development. These data were then imported into SAS 9.4, MySQL, and Excel software for cleaning and analysis (Fig. 1).

Given the spontaneous reporting nature of FAERS, potential duplicates or withdrawn/deleted reports may exist. To address this issue, we performed data cleaning in accordance with the method recommended by the FDA, and the specific operational steps were described in the previous literature [17]. Specifically, duplicate reports were removed by selecting key fields (PRIMARYID, CASEID, and FDA_DT) from the DEMO table. Reports were sorted by CASEID, FDA_DT, and PRIMARYID, retaining for each unique CASEID the entry with the most recent FDA_DT and the highest PRIMARYID value.

To define the target drug user group, only cases where voxelotor and hydroxyurea was listed as the primary suspected cause of the AE were included. During backend analysis, patients were categorized into the target drug population if voxelotor and hydroxyurea were identified as the primary suspected drugs; otherwise, they were assigned to the comparator drug population. To further ensure data integrity, duplicate records with identical identifiers were removed from the DEMO file. Additionally, the REAC file was mapped to MedDRA terminology using PTs for standardized classification [18].

Statistical analysis

A descriptive analysis was conducted to characterize all adverse event reports related to voxelotor and hydroxyurea. Our study uses a case/non-case design similar to a case-control study. We studied adverse events associated

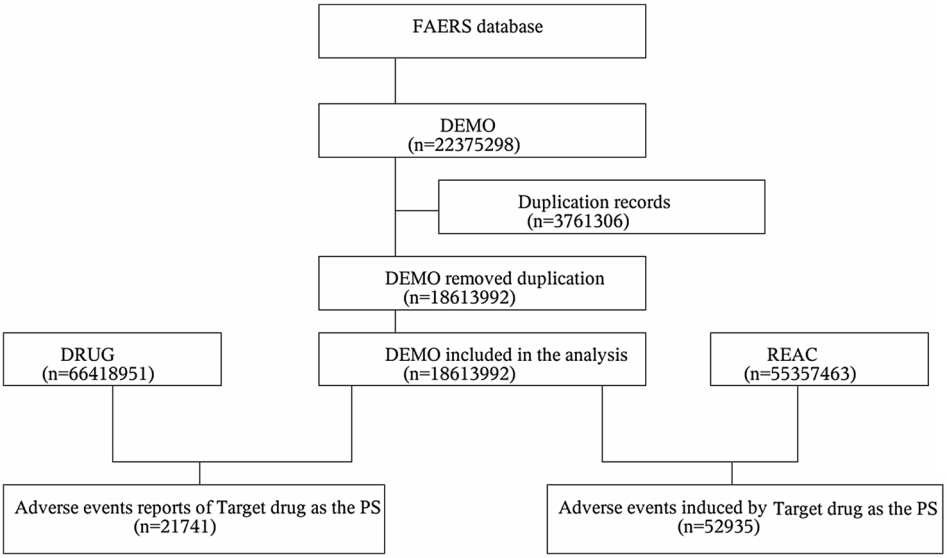

Fig. 1 Flow chart

with the study drug rather than the disease condition. To identify potential safety signals in voxelotor and hydroxyurea, we employed disproportionality analysis, a widely used method in pharmacovigilance studies [19]. Specifically, we applied four major algorithms: Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Multi-item Gamma Poisson Shrinkage (MGPS). Disproportionality analysis was performed using a case/non-case approach to calculate the ROR, PRR, BCPNN, and MGPS values, enabling the detection of potential safety signals. A positive signal was defined as meeting the following criteria: (i) the number of cases ≥ 3; (ii) the lower limit of the ROR 95% confidence interval (CI) > 1; (iii) PRR ≥ 2 with a chi-square value (χ^2) ≥ 4; (iv) the lower limit of the Information Component (IC) 95% CI (IC025) > 0; and (v) the lower limit of the Empirical Bayes Geometric Mean (EBGM) 95% CI (EBGM05) > 2 [20]. For further investigation, we focused on adverse event signals that met the criteria across all four algorithms.

Time to onset (TTO) of voxelotor was defined as the interval between the date of the AE (EVENT_DT) and the start date of the drug administration (START_DT). Only cases with complete and accurate date records were included in the analysis. TTO was stratified, and the median and interquartile range (IQR) were used to quantitatively describe the distribution of adverse event occurrence. Initially, medications meeting four disproportionality analysis methods were categorized based on acute ADRs, delayed ADRs and efficacy-related reports. Specifically, acute ADRs including headache, nausea Cumulative incidence curves and violin plot of TTO for adverse reactions were subsequently analyzed between these groups.

Result

Population characteristics

From 2019 to the first quarter of 2024, a total of 17,627,340 AE reports were submitted to the FAERS database, including 20,902 voxelotor related reports. Of these, 2257 were reported by health care professionals (Table 1). Table 1 summarized the characteristics of AE reports in voxelotor. AE reports were more reported by women than men (59.22% vs. 38.99%), and mainly in young and middle-aged patients (age 18–44) (34.60%). The country with the largest number of AE reports was the United States (96.94%). After excluding reports with unspecific indications, SCD (64.22%) emerged as the most frequently reported therapeutic indication. Additionally, voxelotor demonstrated clinical applications in managing sickle cell anemia with crisis and related symptoms secondary to SCD. In addition, a significant proportion of patients (n = 8,528,40.80%) had serious outcomes, including hospitalization (n = 7191; 34.40%), death (n = 309; 1.48%), life-threatening conditions (n = 31; 0.15%) and disability (n = 9; 0.04%), and other serious outcomes occurred in 1822 cases (8.72%). The highest year reported during the study period was 2022 (45.81%).

Signal of system organ class

In Fig. 2, we compared SOC between voxelotor and hydroxyurea. The significant SOC of voxelotor included Blood and lymphatic system disorders (SOC:1005329, n = 10758); Gastrointestinal disorders (SOC:10017947, n = 9696); Injury, poisoning and procedural complications (SOC:10022117, n = 8799); General disorders and administration site conditions (SOC:10018065, n = 5537); Nervous system disorders(SOC:10029205, n = 2793); Surgical and medical procedures (SOC:10042613, n = 2737);

Table 1 Basic information of voxelotor ADE reports

Characteristics		Case Number, *n*	Case proportion, *n*%
Gender	Female	12,378	59.22
	Male	8149	38.99
	Not Specified	375	1.79
Age(year)	< 18	2932	14.03
	18–44	7233	34.60
	45–64	3011	14.41
	> 64	413	1.98
	Unknow	7313	34.99
Indications (TOP five)	Sickle cell disease	13,423	64.22
	Product used for unknown indication	4673	22.36
	Sickle cell anaemia with crisis	1117	5.34
	Not Specified	709	3.39
	Sickle cell anaemia	294	1.41
Serious outcome	Death	309	1.48
	Hospitalization	7191	34.40
	Life-Threatening	31	0.15
	Disability	9	0.04
	Other Serious Outcome	1822	8.72
Reported countries (top five)	United States	20,263	96.94
	Not Specified	437	2.09
	France	111	0.53
	Germany	37	0.18
	United Kiongdom	32	0.15
Reporting year	2024	629	3.01
	2023	4570	21.86
	2022	9576	45.81
	2021	3487	16.68
	2020	2639	12.63
	2019	1	0.00
Reported Person	Consumer	18,606	89.02
	Health profession	2257	10.8
	Lawyer	2	0.01
	Unknow	37	0.18

Investigations (SOC:10022891, *n* = 2083). Meanwhile, The significant SOC of voxelotor included general disorders and administration site conditions (*n* = 1285); Injury, poisoning and procedural complications (*n* = 1039); Investigations (*n* = 903); Skin and subcutaneous tissue disorders (SOC: 10040785, *n* = 893); Gastrointestinal disorders (*n* = 882). These findings indicated the specific organ systems in which voxelotor or hydroxyurea were mostly common. Hence, nervous system and skin and subcutaneous tissue disorders in voxelotor and hydroxyurea cannont be overlooked in following analysis.In addition, we found that infections and infestations, psychiatric disorders, and hepatobiliary disorders in the SOC mentioned above were new valuable adverse reactions not included in the drug package insert of voxelotor.

Risk signal mining

In Table 2, we listed the top 30 preferred terms (PTs) ranked according to voxelotor positive signal frequency (calculated using a combination of the four analysis methods). Among them, the top five PT of positive signals of target drugs ranked by ROR value were sickle cell anaemia with crisis (ROR = 3782.72, 95%CI = 3638.29-3932.88), acute chest syndrome (ROR = 709.84, 95%CI = 610.88-824.82), sickle cell disease (ROR = 675.08, 95%CI = 554.74-821.52), double heterozygous sickling disorders (ROR = 619.09, 95%CI = 147.95-2590.64) and retinopathy sickle cell (ROR = 238.11, 95%CI = 67.85-835.62). Notably, several unexpectedly significant AEs were identified that were not labeled in the labeling, including skin ulcer (ROR = 5.04, 95%CI = 4.18–6.07), osteonecrosis (ROR = 3.94, 95%CI = 3.30–4.72), priapism (ROR = 29.27, 95%CI = 23.65–36.23) and frequent bowel movements (ROR = 3.86, 95%CI = 3.12–4.79).

Given that certain significant PTs of voxelotor may be associated with the pathological progression of sickle cell disease, to further ascertain whether these PTs represent

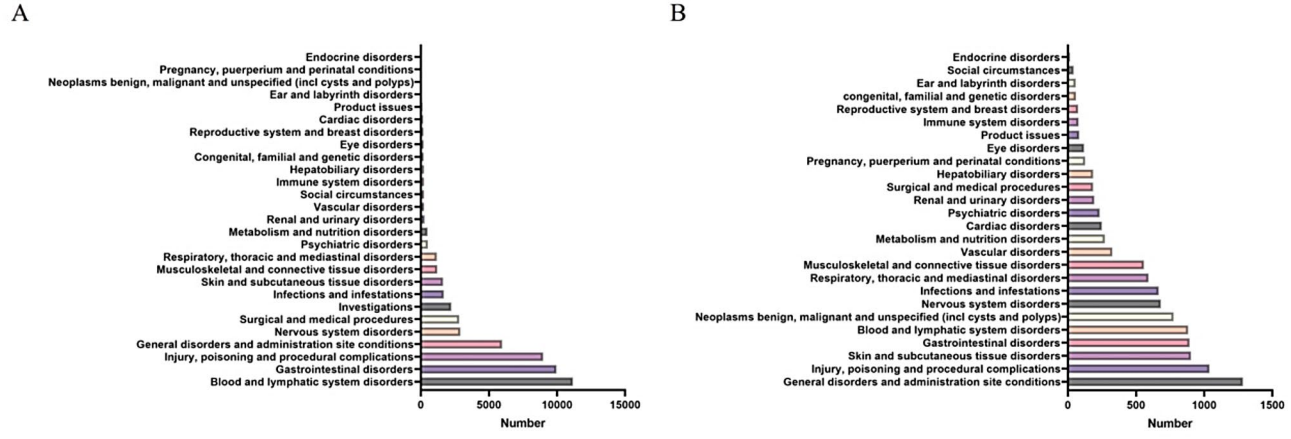

Fig. 2 Comparation between voxelotor and hydroxyurea at SOC level. **A** The number of voxelotor at SOC level. **B** The number of hydroxyurea at SOC level

Table 2 Signal strength of voxelotor reports at the top 30 preferred term (PT) levels

PT	*N*	ROR (95%CI)	PRR (χ^2)	EBGM (EBGM05)	IC (IC025)
Sickle cell anaemia with crisis	10,561	3782.72(3638.29-3932.88)	2995.16(8101356)	9.59(9.44)	768.15(738.82)
Acute chest syndrome	288	709.84(610.88-824.82)	705.81(120362)	8.71(7.22)	419.51(361.03)
Sickle cell disease	165	675.08(554.74-821.52)	672.89(67001.0)	8.67(6.62)	407.67(335.00)
Double heterozygous sickling disorders	3	619.09(147.95-2590.64)	619.05(1156.98)	8.60(0.25)	387.28(92.55)
Hypersplenism	51	146.72(109.41-196.75)	146.57(6456.41)	7.01(4.79)	128.46(95.80)
Retinopathy sickle cell	3	238.11(67.85-835.62)	238.10(575.50)	7.60(0.37)	193.64(55.18)
Pharmacophobia	5	107.49(42.79-270.01)	107.47(477.66)	6.61(1.27)	97.43(38.78)
Emergency care	105	51.89(42.65–63.14)	51.79(4979.75)	5.63(4.80)	49.36(40.56)
Reticulocyte count abnormal	7	76.84(35.65-165.62)	76.83(487.61)	6.16(1.80)	71.58(33.21)
Abdominal symptom	27	43.76(29.77–64.32)	43.73(1081.56)	5.39(3.53)	41.99(28.57)
Sickle cell anaemia	24	42.35(28.15–63.70)	42.33(930.30)	5.35(3.39)	40.70(27.06)
Disease complication	125	33.24(27.81–39.73)	33.16(3777.97)	5.01(4.43)	32.16(26.91)
Therapy cessation	1036	26.43(24.84–28.13)	25.91(24226.5)	4.66(4.54)	25.30(23.78)
Delayed haemolytic transfusion reaction	3	79.37(24.53-256.85)	79.37(215.55)	6.20(0.43)	73.77(22.80)
Product use complaint	295	27.43(24.43–30.80)	27.28(7277.08)	4.73(4.44)	26.60(23.69)
Insurance issue	195	26.28(22.79–30.30)	26.18(4606.36)	4.68(4.30)	25.56(22.16)
Expulsion of medication	11	41.58(22.76–75.98)	41.57(418.70)	5.32(2.38)	40.00(21.89)
Priapism	81	28.07(22.51–35.01)	28.03(2055.26)	4.77(4.05)	27.31(21.90)
Coronavirus infection	152	26.36(22.43–30.97)	26.28(3605.30)	4.68(4.23)	25.65(21.83)
Therapy interrupted	845	21.53(20.10-23.06)	21.19(15938.0)	4.38(4.24)	20.78(19.40)
Haemoglobin increased	76	24.29(19.34–30.50)	24.25(1655.63)	4.57(3.86)	23.72(18.89)
Intentional product misuse to child	3	51.59(16.18–164.50)	51.59(141.74)	5.62(0.43)	49.18(15.42)
Reticulocyte count increased	16	24.28(14.79–39.87)	24.28(348.88)	4.57(2.63)	23.74(14.46)
Product dose omission issue	5223	14.94(14.51–15.37)	13.50(60149.0)	3.74(3.69)	13.34(12.96)
Haemoglobin abnormal	79	15.90(12.73–19.86)	15.88(1084.86)	3.97(3.40)	15.65(12.53)
Infusion	7	22.43(10.61–47.44)	22.43(140.27)	4.46(1.57)	21.97(10.39)
Bone marrow transplant	24	15.86(10.60-23.74)	15.85(328.94)	3.97(2.72)	15.63(10.44)
Blood bilirubin decreased	9	18.95(9.80-36.65)	18.95(150.27)	4.22(1.83)	18.63(9.63)
Central venous catheter removal	7	19.16(9.07–40.47)	19.16(118.27)	4.23(1.51)	18.83(8.91)
Reticulocytopenia	3	28.40(9.02–89.43)	28.40(77.17)	4.79(0.38)	27.66(8.78)

genuine adverse reaction signals for voxelotor, we conducted a systematic analysis of hydroxyurea's established ADRs at the PT level (Table 3). Among them, the top five PT ranked by ROR value in hydroxyurea were skin ulcer (ROR = 769.35, 95%CI = 228.58–2589.46), anaemia (ROR = 569.89, 95%CI = 172.86–1878.83), thrombocytopenia (ROR = 526.3, 95%CI = 335.76–824.98), platelet count increased (ROR = 399.77, 95%CI = 174.15–917.7) and dysphagia (ROR = 349.7, 95%CI = 108.57–1126.4). Furthermore, we compared the frequency of ADRs between voxelotor and hydroxyurea in Fig. 3. Top 5 PTs in voxelotor were sickle cell anaemia with crisis ($n = 10561$), product dose omission issue ($n = 5223$), diarrhea ($n = 3107$), off label use ($n = 2288$) and nausea ($n = 1964$). Top 5 PTs in hydroxyurea were skin ulcer ($n = 150$), anaemia ($n = 137$), thrombocytopenia ($n = 101$), platelet count increased ($n = 95$) and dysphagia ($n = 80$). A comprehensive analysis incorporating both reporting frequency and ROR revealed that skin ulcer and anemia should be classified as inherent clinical manifestations of sickle cell disease rather than drug-related adverse events. Notably, while pharmacovigilance signal detection for voxelotor identified multiple PTs associated with disease progression, hydroxyurea's adverse reaction profile did not demonstrate comparable associations. This marked discrepancy suggests that voxelotor may exert specific mechanistic effects that exacerbate the underlying disease progression in patients. Table S1 and Table S2 list all detectable disproportionate PTs in voxelotor and hydroxyurea.

Off label use analysis

Through the analysis of PTs, we observed that off-label use has emerged as a non-negligible component of voxelotor-related reports, raising concerns about potential unintended applications. In response to these findings, we conducted a focused evaluation of off-label use patterns. After excluding reports with missing or undefined indications (marked as "NA"), a total of 1,238 reports remained for further analysis, we ranked Top10 PTs in Table 4.

Among these, a subset was clearly outside the scope of voxelotor's approved indication, which is limited to the treatment of SCD in patients aged 4 years and older.

Table 3 Signal strength of hydroxyurea reports at the top 30 preferred term (PT) levels

PT	*N*	ROR (95%CI)	PRR (χ^2)	EBGM (EBGM05)	IC (IC025)
Skin ulcer	150	769.35 (228.58–2589.46)	769.13 (2001.21)	668.94 (242.3)	9.39 (7.83)
Anaemia	137	569.89 (172.86–1878.83)	569.72 (1532.86)	512.85 (189.01)	9 (7.47)
Thrombocytopenia	101	526.3 (335.76–824.98)	525.26 (9967.45)	476.54 (327.16)	8.9 (8.25)
Platelet count increased	95	399.77 (174.15–917.7)	399.55 (2212.87)	370.74 (184.97)	8.53 (7.4)
Dysphagia	80	349.7 (108.57–1126.4)	349.6 (976.26)	327.35 (123.01)	8.35 (6.85)
Pancytopenia	75	314.02 (97.86–1007.61)	313.93 (881.81)	295.88 (111.54)	8.21 (6.71)
Platelet count decreased	73	307.74 (95.97–986.8)	307.65 (865.06)	290.29 (109.5)	8.18 (6.69)
Interstitial lung disease	71	263.05 (96.29–718.62)	262.95 (992.9)	250.17 (107.9)	7.97 (6.64)
Acute myeloid leukaemia	58	260.79 (81.74–832.07)	260.72 (738.62)	248.15 (94)	7.96 (6.47)
Malignant neoplasm progression	54	256.45 (80.42–817.81)	256.38 (726.8)	244.22 (92.54)	7.93 (6.44)
Haemoglobin decreased	52	252.24 (79.13–804.04)	252.17 (715.35)	240.4 (91.13)	7.91 (6.42)
Febrile neutropenia	50	229.66 (72.22–730.26)	229.59 (653.52)	219.79 (83.49)	7.78 (6.3)
Squamous cell carcinoma	47	216.72 (68.25–688.16)	216.66 (617.87)	207.91 (79.07)	7.7 (6.22)
White blood cell count increased	46	117.37 (55.47–248.35)	117.3 (789.09)	114.7 (61.26)	6.84 (5.81)
Sickle cell anaemia with crisis	46	95.63 (71.16–128.51)	95.23 (4119.43)	93.51 (73.03)	6.55 (6.12)
Actinic keratosis	45	87.92 (28.08–275.31)	87.9 (253.39)	86.44 (33.26)	6.43 (4.97)
Splenomegaly	41	83.65 (37.33–187.45)	83.6 (481.82)	82.28 (41.88)	6.36 (5.26)
Foetal exposure during pregnancy	40	81.13 (40.34–163.16)	81.07 (622.8)	79.82 (44.49)	6.32 (5.35)
Stomatitis	40	70.66 (29.23–170.82)	70.63 (338.54)	69.68 (33.29)	6.12 (4.93)
Basal cell carcinoma	39	65.05 (38.38–110.24)	64.96 (870.7)	64.16 (41.27)	6 (5.25)
Respiratory failure	38	63.7 (36.04–112.6)	63.63 (730.69)	62.86 (39.03)	5.97 (5.17)
Tumour lysis syndrome	38	59.47 (22.19–159.39)	59.45 (227.23)	58.78 (25.76)	5.88 (4.58)
Squamous cell carcinoma of skin	36	54.77 (24.5–122.47)	54.74 (313.22)	54.17 (27.63)	5.76 (4.66)
Mucosal inflammation	35	54.3 (37.4–78.83)	54.16 (1445.72)	53.6 (39.24)	5.74 (5.2)
Pleural effusion	30	53.5 (35.46–80.72)	53.39 (1170.21)	52.85 (37.46)	5.72 (5.13)
Cerebral infarction	29	47.64 (15.28–148.51)	47.62 (135.68)	47.19 (18.23)	5.56 (4.11)
Myelofibrosis	28	47.32 (19.61–114.18)	47.3 (224.55)	46.88 (22.43)	5.55 (4.37)
Impaired healing	27	47.06 (19.51–113.55)	47.04 (223.27)	46.62 (22.31)	5.54 (4.36)
Mouth ulceration	24	46.49 (14.91–144.9)	46.47 (132.29)	46.06 (17.79)	5.53 (4.07)
Myelodysplastic syndrome	23	45.88 (28.45–73.98)	45.81 (738.49)	45.41 (30.44)	5.5 (4.82)

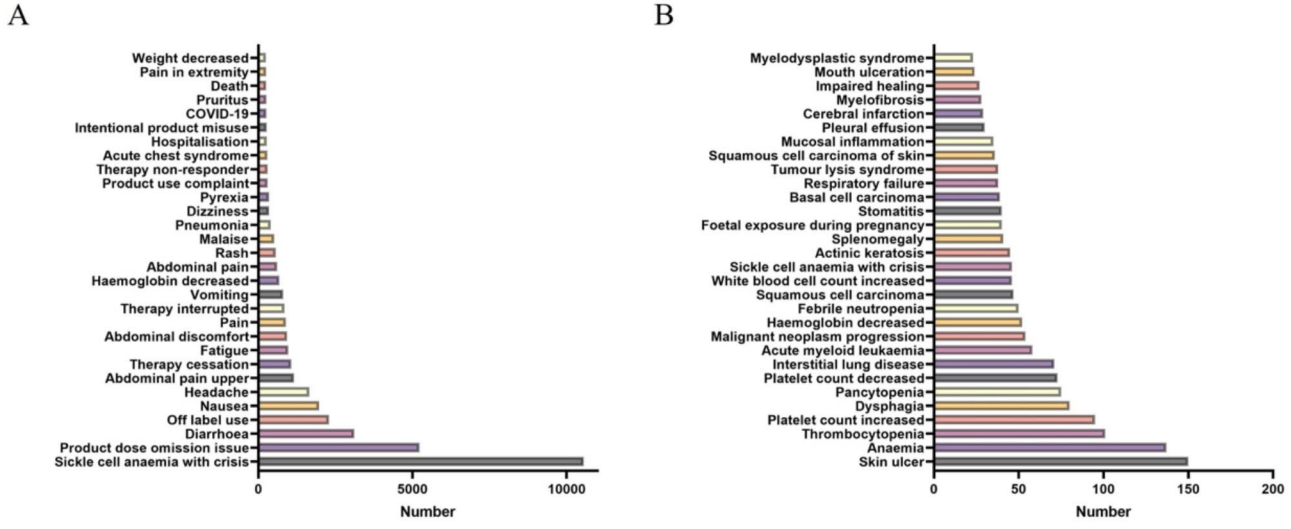

Fig. 3 Comparation positive signal frequency of voxelotor and hydroxyurea. **A** The number of voxelotor at PT level. **B** The number of hydroxyurea at PY level

Table 4 The frequency of off label use in voxelotor

PT	Number	Percent
Haemoglobin C disease	380	30.7%
Haemolytic anaemia	316	25.5%
Anaemia	172	13.9%
Thalassaemia beta	122	9.9%
Haemoglobin decreased	41	0.3%
Full blood count decreased	27	0.2%
Haemochromatosis	21	0.2%
Pain	22	0.2%
Iron metabolism disorder	13	0.1%
Haemoglobin abnormal	12	0.1%

Specifically, 380 reports involved haemoglobin C disease and 122 involved beta-thalassaemia—two distinct haemoglobinopathies that are not part of the drug's labeled use. These cases represent clear instances of off-label use. While both conditions share certain pathophysiological features with SCD, such as chronic hemolysis and anemia, their inclusion in this dataset suggests exploratory or unapproved clinical application of voxelotor. Other frequently reported conditions, including haemolytic anaemia ($n = 316$), unspecified anaemia ($n = 172$), and laboratory abnormalities such as decreased haemoglobin ($n = 41$) or reduced full blood count ($n = 27$), may reflect clinical manifestations or complications of SCD. As such, their classification as off-label is less definitive without further clinical context. Likewise, reports related to pain, iron metabolism disorders, and haemoglobin abnormalities may be indirectly related to the disease spectrum and thus remain ambiguous in terms of labeling relevance.

Time-to-onset analysis

TTO analysis for voxelotor-related events revealed substantial differences across acute ADRs, delayed ADRs, and efficacy-related reports, suggesting heterogeneous temporal patterns (Fig. 4).

To begin with, acute ADRs were reported significantly earlier than the other categories, with a median TTO of just 1 day (interquartile range [IQR]: 0–87.75). Notably, over 75% of acute ADRs were reported within the first three months of treatment, and the earliest events occurred on the day of drug initiation. Although the maximum reported TTO extended to 2512 days, the cumulative curve demonstrated a sharp early rise followed by a plateau, indicating that acute ADRs predominantly cluster in the early treatment phase. In contrast, delayed ADRs exhibited a markedly later onset, with a median TTO of 189.5 days (IQR: 79.5–280.25). While the number of cases was relatively limited ($n = 24$), the maximum onset time reached 698 days, highlighting the potential for late-emerging toxicities. The broader temporal distribution of these events emphasizes the importance of prolonged safety monitoring beyond the acute phase of treatment. Meanwhile, efficacy-related reports demonstrated the widest temporal range, with a median TTO of 213 days (IQR: 59–462) and a maximum onset of 2931 days. This extended distribution may reflect the time-dependent nature of therapeutic response assessment, which often requires long-term follow-up and multifactorial evaluation.

Discussion

In general, most previous studies of safety and efficacy were based on small sample clinical studies and pre-clinical studies [21–23]. However, limited experimental design and the small sample size can lead to inaccurate conclusions. FAERS is a publicly available database, which provided tens of millions of valuable AE data collected from medical product manufacturers, health professionals and the public to researchers. A large sample of real-world data increased the objectivity and generalizability of this study. Therefore, we collected and evaluated the pharmacovigilance of voxelotor by using FAERS database.

SCD, an inherited hemoglobin disorder, is characterized by hemoglobin polymerization under hypoxic conditions within capillary beds, resulting in sickle-shaped

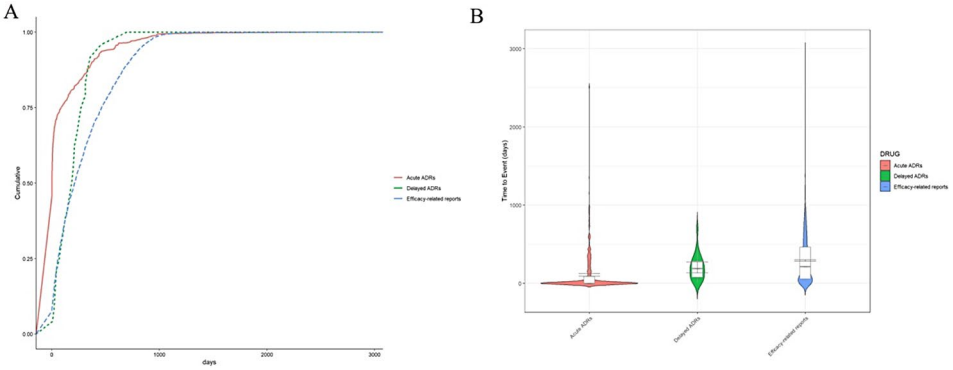

Fig. 4 Time to onset time analysis. **A** Cumulative curve of voxelotor ADRs according to acute ADRs, delayed ADRs and efficacy related reports. **B** Violin plot of voxelotor ADRs according to acute ADRs, delayed ADRs and efficacy related reports

deformation of red blood cells (RBCs), progressive multiorgan damage, and increased mortality [24]. Distinct from normal erythrocytes, sickled cells exhibit upregulated adhesion molecules that promote adhesion to endothelial surfaces. These rigid, fragile RBCs undergo accelerated hemolysis, leading to compensatory elevation of reticulocytes (immature erythrocytes) while simultaneously contributing to localized endothelial dysfunction through vaso-occlusive mechanisms [25].

Clinical studies have demonstrated that voxelotor significantly elevates hemoglobin levels and reduces hemolytic markers in patients with SCD [10, 21], highlighting its potential as a disease-modifying therapy, offering a promising approach to ameliorate the clinical manifestations and complications associated with SCD. However, the mechanisms underlying its AEs, such as osteonecrosis and priapism, remain poorly understood.

Priapism, which affects approximately 40% of male SCD patients, may result from dysfunction in the nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) signaling pathways, as well as the excessive release of heme, both of which are known to significantly contribute to the pathogenesis of priapism in SCD [26]. These findings suggest that while voxelotor effectively targets hemoglobin S polymerization, its impact on tissue oxygenation and blood flow dynamics may contribute to certain AEs. Given the significantly elevated risk of priapism in adolescent patients with sickle cell disease, targeted health education interventions initiated from childhood or early adolescence, coupled with enhanced recognition of early clinical manifestations, are critical for preventing irreversible complications [27]. A multicenter collaborative initiative led by Guy's Hospital developed an educational video on priapism tailored for adolescent males, aiming to improve disease literacy through patient-friendly media and reduce stigma associated with symptom reporting, thereby facilitating early medical intervention [28]. We recommend that healthcare institutions and public health agencies worldwide adopt this innovative model by developing culturally adapted multi-media educational tools (e.g., animations, interactive apps) and establishing standardized patient education frameworks through interdisciplinary collaboration, which may systematically improve the management of this complication.

Osteonecrosis warrants particular attention as a potential adverse drug event. Although current evidence has not conclusively established direct effects of voxelotor on bone metabolic pathways, our study reveals that no similar reports were documented in the ADRs of hydroxyurea. This discrepancy suggests that voxelotor may possess unique mechanisms affecting bone tissue. The underlying pathological mechanisms might involve voxelotor's enhancement of hemoglobin oxygen affinity, potentially altering oxygen partial pressure gradients in bone marrow microcirculation [29, 30]. Such alterations could induce localized tissue hypoxia or hemodynamic disturbances, thereby initiating ischemic bone injury cascades. Therefore, in clinical practice, long-term medication patients should undergo regular bone mineral density (BMD) testing and osteochondral MRI screening. Furthermore, future studies should utilize animal models to verify the dose-response relationship between oxygen partial pressure gradient alterations and osteonecrosis, while conducting prospective cohort studies to elucidate the real-world incidence rates and risk factors.

In terms of demographic difference, our study revealed a higher incidence of AEs in female patients (59.22%) compared to males (38.99%). This disparity may be attributed to hormonal influences on drug metabolism or immune responses. Additionally, epidemiological data indicate that SCD affects both genders equally, but women may have higher healthcare utilization rates, potentially leading to increased reporting of AEs [31]. Further research is needed to explore whether biological factors (e.g., hormonal differences) or healthcare-seeking behaviors contribute to this observed disparity. Regarding age distribution, young and middle-aged patients (18–65 years) accounted for the majority of AE reports (34.60%), consistent with the median survival age of SCD patients (45–65 years) reported in previous studies [32–34]. However, the higher incidence of AEs in this population may also reflect increased disease activity and treatment intensity rather than a direct effect of voxelotor. Future studies should compare AE rates in young patients with the overall SCD population to determine whether the observed patterns align with theoretical exposure rates.

In summary, voxelotor was a sickle hemoglobin-polymerization inhibitor approved for the treatment of SCD in patients, which acted by modifying the affinity between Hb and oxygen [35, 36]. Several studies demonstrated clinical benefit of voxelotor in SCD treatment, which provided significant, durable increases in haemoglobin concentrations and reductions in markers of haemolysis and a favourable safety profile [10, 21, 37].

There were, of course, a number of limitations to this study. First of all, causality cannot be definitively established due to the spontaneous and voluntary nature of adverse event reporting. The FAERS database relies on reports submitted by healthcare professionals, manufacturers, and patients, which may lead to underreporting or overreporting of certain events, introducing potential reporting bias. Secondly, Furthermore, there is a potential overrepresentation of female patients in the dataset, which could affect the generalizability of the findings to the broader patient population. Finally, despite comparing voxelotor with hydroxyurea to exclude some

disease-related adverse events, we were unable to fully distinguish between efficacy-related reactions and true adverse drug reactions. Further studies that can distinguish between efficacy-related events and genuine ADRs by clinical trial are warranted to provide a clearer understanding of voxelotor's safety profile.

Conclusion

The study leveraged FAERS data to evaluate voxelotor's safety in treating SCD, revealing a higher prevalence of adverse events in females and young to middle-aged patients. Significant systems affected include blood, gastrointestinal, and nervous systems. The analysis identified common adverse events such as nausea and diarrhea, alongside unlisted ones like priapism and osteonecrosis. The study underscored the reliability of using real-world data to enhance pharmacovigilance, despite limitations like potential reporting bias and the inability to establish causality. Findings highlighted the need for ongoing monitoring and further investigation into voxelotor's long-term safety and efficacy. Future research should be focused on addressing these limitations to validate the drug's benefit-risk profile comprehensively.

Abbreviations

SCD	Sickle cell disease
FAERS	The FDA Adverse Event Reporting System
ROR	Reporting Odds Ratio
PRR	Proportional Reporting Ratio
BCPNN	Bayesian Confidence Propagation Neural Network
MGPS	Multi-item Gamma Poisson Shrinkage
SOC	System organ categories
HbS	Hemoglobin S
PT	Preferred terms
IQR	Interquartile range

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

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Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval

The FAERS datasets are publicly accessible and anonymized, thus obviating the need for ethical approval in our current study.

Consent to participate

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet (lond Engl). 2010;376:2018–31.
2. Brandow AM, Liem RI. Advances in the diagnosis and treatment of sickle cell disease. J Hematol Oncol. 2022;15:20.
3. Serjeant GR. The natural history of sickle cell disease. Cold Spring Harb Perspect Med. 2013;3:a011783.
4. Pace BS, Starlard-Davenport A, Kutlar A. Sickle cell disease: Progress towards combination drug therapy. Br J Haematol. 2021;194:240–51.
5. Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the multicenter study of hydroxyurea in sickle cell anemia. N Engl J Med. 1995;332:1317–22.
6. Tzounakas VL, Valsami SI, Kriebardis AG, Papassideri IS, Seghatchian J, Antonelou MH. Red cell transfusion in paediatric patients with thalassaemia and sickle cell disease: current status, challenges and perspectives. Transfus Apher Sci: Off J World Apher Assoc: Off J Eur Soc Haemapheresis. 2018;57:347–57.
7. Darshana T, Rees D, Premawardhena A. Hydroxyurea and blood transfusion therapy for sickle cell disease in South Asia: inconsistent treatment of a neglected disease. Orphanet J Rare Dis. 2021;16:148.
8. Achebe MO, Hassab HM, Al-Kindi S, Brown C, Telfer P, Biemond BJ, et al. Over 4 years of safety and efficacy with voxelotor treatment for patients with sickle cell disease: updated results from an open-label extension of the phase 3 HOPE trial. Blood. 2023;142:2527.
9. Blair HA. Voxelotor: First approval. Drugs. 2020;80:209–15.
10. Vichinsky E, Hoppe CC, Ataga KI, Ware RE, Nduba V, El-Beshlawy A, et al. A phase 3 randomized trial of voxelotor in sickle cell disease. N Engl J Med. 2019;381:509–19.
11. Minniti CP, Knight-Madden J, Tonda M, Gray S, Lehrer-Graiwer J, Biemond BJ. The impact of voxelotor treatment on leg ulcers in patients with sickle cell disease. Am J Hematol. 2021;96:E126–8.
12. Howard J, Vichinsky E, Knight-Madden J, Tonda M, Washington C, Tong B, et al. Correlation of voxelotor exposure with hemoglobin response and measures of hemolysis in patients from the HOPE study. Blood. 2019;134:1020.
13. Lemon N, Sterk E, Rech MA. Acute venous thromboembolism after initiation of voxelotor for treatment of sickle cell disease. Am J Emerg Med. 2022;55:225.e1-225.e3.
14. Migotsky M, Beestrum M, Badawy SM. Recent advances in sickle-cell disease therapies: A review of voxelotor, crizanlizumab, and L-glutamine. Pharm (Basel). 2022;10:123.
15. Liu Y, Dong C, He X, Shu Y, Wu P, Zou J. Post-marketing safety of Vemurafenib: a real-world pharmacovigilance study of the FDA adverse event reporting system. J Pharm Pharm Sci: Publ Can Soc Pharm Sci Soc Can Sci Pharm. 2022;25:377–90.
16. Liu M, Gu L, Zhang Y, Zhou H, Wang Y, Xu Z-X. A real-world disproportionality analysis of mesalazine data mining of the public version of FDA adverse event reporting system. Front Pharmacol. 2024;15:1290975.
17. Zou T, Li Z, Wang T, Deng S, Wang S, Hua Y. A real-world disproportionality analysis of the US food and drug administration (FDA) adverse event reporting system (FAERS) events for durvalumab. BMC Pharmacol Toxicol. 2024;25:97.
18. Zou S-P, Yang H-Y, Ouyang M-L, Cheng Q, Shi X, Sun M-H. A disproportionality analysis of adverse events associated to pertuzumab in the FDA adverse event reporting system (FAERS). BMC Pharmacol Toxicol. 2023;24:62.

19. He W, Wang Y, Chen K. A real-world pharmacovigilance study of FDA adverse event reporting system events for diazepam. Front Pharmacol. 2024;15:1278442.
20. Zhou C, Peng S, Lin A, Jiang A, Peng Y, Gu T, et al. Psychiatric disorders associated with immune checkpoint inhibitors: A pharmacovigilance analysis of the FDA adverse event reporting system (FAERS) database. Eclinicalmedicine. 2023;59:101967.
21. Howard J, Ataga KI, Brown RC, Achebe M, Nduba V, El-Beshlawy A, et al. Voxelotor in adolescents and adults with sickle cell disease (HOPE): Long-term follow-up results of an international, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Haematol. 2021;8:e323–33.
22. Haroun E, Dutta D, Lim SH. Effects of GBT1118, a voxelotor analog, on intestinal pathophysiology in sickle cell disease. Br J Haematol. 2023;202:184–94.
23. Dufu K, Williams AT, Muller CR, Walser CM, Lucas A, Eaker AM, et al. Increased hemoglobin affinity for oxygen with GBT1118 improves hypoxia tolerance in sickle cell mice. Am J Physiol Heart Circ Physiol. 2021;321:H400–11.
24. Piel FB, Steinberg MH, Rees DC. Sickle cell disease. N Engl J Med. 2017;376:1561–73.
25. Sparkenbaugh E, Pawlinski R. Prothrombotic aspects of sickle cell disease. J Thromb Haemost: JTH. 2017;15:1307–16.
26. Silveira THR, Calmasini FB, de Oliveira MG, Costa FF, Silva FH. Targeting Heme in sickle cell disease: New perspectives on priapism treatment. Front Physiol. 2024;15:1435220.
27. Emmanuel A, Moussa A, Kesse-Adu R, Shabbir M. A contemporary review of the management strategies for sickle cell disease related ischaemic and stuttering priapism. Int J Impot Res. 2024:1–7.
28. Read ET. Mar 3 min. Priapism in sickle cell disease. Sickle-cell.com. https://sickle-cell.com/complications/priapism. Accessed 22 2025.
29. Henry ER, Metaferia B, Li Q, Harper J, Best RB, Glass KE, et al. Treatment of sickle cell disease by increasing oxygen affinity of hemoglobin. Blood. 2021;138:1172–81.
30. Li C, Zhao R, Yang H, Ren L. Construction of bone hypoxic microenvironment based on bone-on-a-chip platforms. Int J Mol Sci. 2023;24:6999.
31. Kanter J, Kruse-Jarres R. Management of sickle cell disease from childhood through adulthood. Blood Rev. 2013;27:279–87.
32. Thein MS, Igbineweka NE, Thein SL. Sickle cell disease in the older adult. Pathol (Phila). 2017;49:1–9.
33. Hamideh D, Alvarez O. Sickle cell disease related mortality in the United States (1999–2009). Pediatr Blood Cancer. 2013;60:1482–6.
34. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med. 1994;330:1639–44.
35. AlDallal SM. Voxelotor: A ray of hope for sickle disease. Cureus. 2020;12:e7105.
36. Torres L, Conran N. Emerging pharmacotherapeutic approaches for the management of sickle cell disease. Expert Opin Pharmacother. 2019;20:173–86.
37. Howard J, Hemmaway CJ, Telfer P, Layton DM, Porter J, Awogbade M, et al. A phase 1/2 ascending dose study and open-label extension study of voxelotor in patients with sickle cell disease. Blood. 2019;133:1865–75.

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