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Real-World Treatment Patterns in Sickle Cell Disease (SCD) in Europe, Africa, Eastern Mediterranean Region (EMR), and India: A Systematic Literature Review (SLR)

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INTRODUCTION

- Sickle cell disease (SCD) describes a group of inherited disorders of erythrocytes. In SCD, erythrocytes turn into a rigid sickle shape (versus the typical disc shape), which causes the cells to break down prematurely, limiting normal blood flow and causing a variety of clinical events, particularly anemia and vaso-occlusive crisis.
- Life-threatening complications in SCD patients include stroke, acute chest syndrome, splenic sequestration, and multi-system organ failure.
- Globally, there are over 500,000 infants born with SCD every year, with the highest numbers in Africa, India, and the Eastern Mediterranean regions. There are currently nearly eight million people globally living with SCD.[1]
- Hydroxyurea has been used for decades to reduce the frequency of vaso-occlusive crises. Opioids are used for pain management, and iron chelation therapies are used to mitigate the risk of iron overload in patients undergoing frequent blood transfusions. However, the real-world use of these treatments across geographies has not been comprehensively reviewed.

OBJECTIVE

- To describe the real-world pharmacologic treatment patterns in patients with SCD in Europe, Africa, the Eastern Mediterranean Region (EMR), and India.

METHODS

- A systematic literature review (SLR) was performed on January 22, 2024, in Embase, MEDLINE, and the Cochrane Database of Systematic Reviews for articles published in English language on or after January 2008 according to the SLR protocol using comprehensive search strings (PROSPERO registration CRD42023487289). Grey literature included conference proceedings from January 2018 to the present. Studies of interest were of observational design that described treatment use, sequence, duration, and untreated periods in patients from Europe, Africa, EMR, and India.

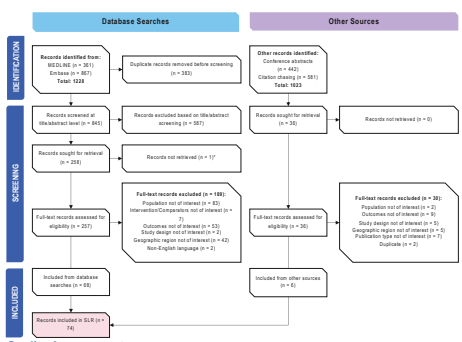
RESULTS

- From 845 unique records identified from database searches and 36 records identified from grey literature, 74 records were selected in the SLR according to the protocol, including five SLRs, 61 publications describing unique studies (i.e., primary publications), and eight secondary publications (i.e., analyses and publications related to the study with existing primary publication; **Figure 1**).

Results for the 61 primary studies include the following (**Table 1**):

- Data collection dates: 30 studies collected data within 2015–2024, 16 studies collected data from before 2015 and up to 2024, five studies collected data up to 2014, and 10 studies did not report data collection dates.
- Countries: 37 studies collected data from one of the following five countries: Saudi Arabia (12 studies), the UK (11 studies), Italy (5 studies), Nigeria (5 studies), and France (4 studies). In the remaining 24 studies, Angola, Belgium, the Democratic Republic of Congo, Egypt, Germany, Ghana, India, Lebanon, Mali, the Netherlands, Oman, Qatar, Sudan, Tanzania, and Turkey were represented in 1–2 studies each. In addition, three studies reported data from multiple countries.
- Study designs: 34 studies were retrospective cohorts; the remainder included prospective cohorts (14 studies), cross-sectional (12 studies), and both cross-sectional and retrospective data (1 study).
- SCD genotypes: 50 studies enrolled SCD patients of any genotype, one enrolled patients with SCD or HbS-β+thal, seven enrolled HbSS only, and three enrolled HbSS or HbS-βthal.

Figure 1. PRISMA Diagram



Quality Assessment

- One inclusion criterion for this review required that studies be based on medical records to eliminate inaccuracies due to self-report or to selection bias in survey-based studies. Reported outcomes among patients from regions with limited health care access and pharmacy services may not be fully representative of all patients with SCD in those countries. Thirty-seven of the 61 studies reported information from a single timepoint (either baseline or not specified).

RESULTS (continued)

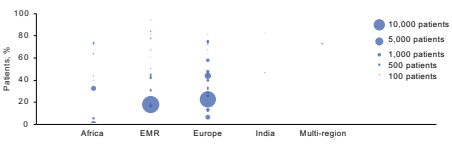
Table 1. Studies Included in the SLR

Author, Year	Data Source	Data Collection Dates	Study Country	Study Design	N
Africa					
Santos, 2024[62]	Hospital Pediatrico David Bernardino	2019 to 2022	Angola	Prospective	215
Kabuyi, 2023[36]	Centre de Médecine Mixte et d'Anémie SS	Aug 2017 to May 2020	DR Congo	Prospective	166
Marfo, 2023[40]	Nationwide Medical Insurance Claims Database	Jan 2015 to Mar 2021	Ghana	Retrospective	2,863
Odoom, 2022[46]	Komfo Anokye Teaching Hospital (KATH), Paediatric SCD Clinic	Oct 2021 to Jan 2022	Ghana	Cross-sectional	421
Anderson, 2023[13]	Koutiala Women's and Children's Hospital	Mar 2019 to Mar 2023	Mali	Prospective	81
Adewoyin, 2017[7]	University of Benin Teaching Hospital	May 2015 to Jul 2015	Nigeria	Cross-sectional	60
Chianumba, 2022[22]	Sickle Pan African Research Consortium (SPARCO) registry	Apr 2021 to Jul 2021	Nigeria	Cross-sectional	1,983
Nnebe-Agumadu, 2021[45]	University of Abuja Teaching Hospital	2017 to 2019	Nigeria	Retrospective Cohort	180
Okoye, 2022[47]	NR	NR	Nigeria	Retrospective	509
Oluesan, 2017[48]	Ekiti State University Teaching Hospital	Jan 2014 to Dec 2014	Nigeria	Retrospective	202
Talha, 2022[26]	Gaafar Ibnauf Referral Hospital	Apr 2018 to Jul 2018	Sudan	Retrospective	207
Ambrose, 2023[12]	Bugando Medical Centre	Oct 2020 to Apr 2021	Tanzania	Retrospective	87
Eastern Mediterranean Region					
Tantawy, 2013[37]	Pediatric Hematology Clinic	Mar 2010 to Nov 2011	Egypt	Prospective	60
Adlette Inati, 2022[4]	NINI hospital in North Lebanon	May 2018 to Apr 2020	Lebanon	Retrospective	136
Adlette Inati, 2022[28]					
Al Fadhali, 2019[5]	Sultan Qaboos University Hospital	Jun 2017 to Jan 2019	Oman	Cross-sectional	85
Jose, 2019[35]	Nizwa Hospital, Oman	Jan 2016 to May 2016	Oman	Cross-sectional	298
Alshurafa, 2022[41]	National Center for Cancer care & research hospital , Hamad Medical Corporation	Jan 2011 to Jan 2021	Qatar	Cross-sectional	49
Abd El-Ghany, 2021[1]	Ibn Sina, Al Jedaani Al Safa and New Al Jedaani Hospitals patient medical records	Jan 2018 to Dec 2019	Saudi Arabia	Retrospective	94
Al-Ali, 2021[6]	King Fahd Hospital, Al-Ahsa or King Fahd Hospital of the University, Imam Abdulrahman Bin Faisal University, Dammam	2016 to 2019	Saudi Arabia	Prospective	780
Ali, 2021[7]	Tertiary hospital and outpatient hematological clinics	NR	Saudi Arabia	Cross-sectional	110
Alkhalifah, 2022[4]	University-affiliated tertiary care center	Jan 2021 to Nov 2021	Saudi Arabia	Retrospective	156
Almalki, 2023[9]	Tertiary health care center, KAUH	May 2006 to May 22	Saudi Arabia	Cross-sectional	414
Alotaibi, 2023[16]	King Abdulaziz Medical City-Jeddah	Jan 2018 to Dec 2020	Saudi Arabia	Retrospective	76
Azmet, 2020[17]	Hematology Department, King Saud Medical City	Jan 2012 to Jul 2017	Saudi Arabia	Retrospective	416
Balsalmal, 2022[18]	Department of Pediatric Hematology King Saud Medical City	Jan 2014 to Dec 2019	Saudi Arabia	Retrospective	47
Elghazaly, 2019[20]	Outpatient clinics at King Saud Medical City	May 2017 to Jan 2018	Saudi Arabia	Retrospective	152
Ezzat, 2022[30]	Saudi Ministry of Health	2019 to 2021	Saudi Arabia	Prospective	22,956
Mohzari, 2022[42]	King Saud Medical City	Jan 2019 to Dec 2020	Saudi Arabia	Retrospective	43
Sendy, 2023[52]	King Saud Medical City	Jan 2021 to Dec 2021	Saudi Arabia	Retrospective	70
Europe					
Peresse, 2019[53]	Hôpital Universitaire des Enfants Reine Fabiola	NR to Mar 2019	Belgium	Retrospective	59
Wambacq, 2021[74]	Belgian SCD registry	NR to May 2021	Belgium	Prospective	1029
Brousse, 2023[54]	French national claims database (Système National des Données de Santé – SNDS)	Jan 2012 to Dec 2018	France	Retrospective	20,412
Beillat, 2023[19]		Jan 2016 to Dec 2018			151
Couque, 2016[23]	National reference laboratory of Robert-Debre Hospital	1995 to 2009	France	Retrospective	1,033
Leleu, 2021[40]	French health insurance information system	2011 to 2016	France	Cross-sectional	414
Galacteros, 2019[32]	The European Sickle Cell Disease Cohort	Jan 2009 to NR	France, Germany, Greece, and Italy	Prospective	1,906
Galacteros, 2020[31]					
Asemissen, 2023[14]	NR	NR	Germany	Retrospective	80
Kunz, 2021[38] Kunz, 2021[39]	Allgemeine Ortskrankenkasse, Public Health Insurance	2011 to 2019	Germany	Retrospective	3,200
De Franceschi, 2022[24]	Administrative databases used by the Italian NHS	Jan 2010 to Dec 2017	Italy	Retrospective	1,816
De Franceschi, 2021[25]					
Munaretto, 2023[44]	National Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP) cohort	Jan 2013 to Jan 2018	Italy	Retrospective	122,
Munaretto, 2019[43]					
Reggiani, 2021[27]	NR	Oct 2007 to Dec 2020	Italy	Retrospective	182
Reggiani, 2022[29]	The SCD Natural History Study - Pediatric SCD Reference Center of Padua	NR to Dec 2020	Italy	Prospective	182
Rigano, 2018[58]	Hematology Centers	NR	Italy	Retrospective	652
De Ligt, 2023[57]	NR	Jan 2010 to Sep 2022	Netherlands	Prospective	209
Aydin, 2021[16]	Blood Disease Center of Hatay State Hospital	Apr 2018 to Apr 2019	Turkey	Cross-sectional	53
Gurkan, 2021[33]	The National Hemoglobinopathy Register of the Turkish Society of Hematology	NR	Turkey	Prospective	656
Adesanya, 2021[2]	NR	NR	UK	Retrospective	NR
Ame de Kreuk, 2023[56]	UK Natural History Study	NR	UK	Prospective	241
Dhanji, 2020[59]	Trust's audit committee	NR	UK	Retrospective	55
Oyesanya, 2022[60]	Royal London Hospital	Jan 2010 to Jun 2019	UK	Retrospective	69
Park, 2019[61]	Tertiary haemoglobinopathy center	Mar 2005 to Mar 2018	UK	Retrospective	93
Pitsilides, 2021[54]	Sheffield Teaching Hospitals	Sep 2019 to Sep 2020	UK	Retrospective	74
Ragheb, 2020[34]	NR	2015 to 2019	UK	Retrospective	23
Sangarapillai, 2020[55]	East London Newborn Cohort Study	1983 to NR 2015 to 2018	UK	Prospective	266 175
Tsouana, 2015[50]	East London clinical haemoglobinopathy network	May 2007 to Dec 2012	UK	Retrospective	62
Tsouana, 2020[51] Tsouana, 2021[49]	District general hospital	Jul 2016 to Jul 2019	UK	Retrospective	52 32
Tsouana, 2022 (A)[52]	Departmental database	NR	UK	Retrospective	154
Tsouana, 2022 (B)[53]	Paediatric SCD database	NR	UK	Retrospective	11
India					
Pazare, 2023[12]	Tertiary care hospital	Sep 2019 to Aug 2021	India	Cross-sectional	94
Prajapati, 2022[25]	Department of Paediatrics at Gandhi Medical College and associated Hamidia Hospital Bhopal	Jan 2020 to Jun 2021	India	Prospective	31
Multi-regional					
Cela, 2018[21]	Spain: Hemoglobinopathy Pediatric Spanish Registry; Gulf: NR	Spain: Jan 2014 to May 2015 Gulf: Feb 2014 to Aug 2016	Spain, Qatar, UAE, and Oman	Spain: Retrospective Gulf: Cross-sectional	Spain: 615 Gulf: 410
Silva-Pinto, 2022[64]	Managed Access Program (MAP)	NR to Feb 2022	Brazil, Italy, Spain, Israel	Retrospective	87

Hydroxyurea Use and Adherence, Compliance, and Interruption

- Estimates for hydroxyurea utilization (49 of 61 studies), the current standard of care SCD treatment, ranged from 0.3% (Marfo, 2023)[41] to 94% (Sendy, 2023)[63] of patients without any clear geographic patterns. In 20 of the 49 hydroxyurea studies, >50% of patients used hydroxyurea (**Figure 2**).

Figure 2. Hydroxyurea Use



Use of hydroxyurea across the included studies according to geographic region. Bubbles indicate relative population size within each study.

- Hydroxyurea adherence, compliance, and interruption were reported using different or non-reported definitions across 10 studies (**Table 2**). Among these studies, reasons for poor adherence,compliance, or discontinuation included a perceived lack of benefit, adverse events, cost, access, and clinical complications/contraindications.[3,10,32,35,36,45]

Table 2. Hydroxyurea Adherence and Compliance

Author, Year	Country	Data Collection Dates	Patient Number, n	Follow-up Period	Adherence, Compliance, and Interruptions, % (Definition)
Africa					
Kabuyi, 2023[36]	Democratic Republic of Congo	2017 to 2020	70	24 months	Adherence: 36% (Adherence = continued in study)
Adewoyin, 2017[7]	Nigeria	2015 to 2015	60	Not reported	Regular: 20% (Compliance not defined)
Nnebe-Agumadu, 2021[45]	Nigeria	2017 to 2019	180	15 months	Adherence: 89% (Adherence = taking daily)
Eastern Mediterranean Region					
Tantawy, 2013[37]	Egypt	2010 to 2011	60	12 months (mean)	Compliance: 82% (Compliance = receipt of >75% of prescribed dose/kg)
Jose, 2019[35]	Oman	2016 to 2016	298	5 months	Adherence: 83% (Adherence = self-report of taking drug all or nearly all the time)
Alshurafa, 2022[41]	Qatar	2011 to 2021	49	Not reported	Compliance: 80% (Compliance not defined)
Alotaibi, 2023[16]	Saudi Arabia	2018 to 2020	76	Not reported	Not poor compliance: 80% (Compliance not defined)
Azmet, 2020[17]	Saudi Arabia	2012 to 2017	128	Not reported	Compliance: 77% (Compliance not defined)
Europe					
Couque, 2016[23]	France	1995 to 2009	1,033	6,776 patient-years	Compliance: 94% (Compliance = attended >1 medical visit, complied with vaccine schedule, and/or took preventative medications)
Multi-regional					
Galacteros, 2019[32]	France, Germany, Greece, and Italy	2009 to NR	1,906	Up to 10 years	No interruptions: 68% (Interruption = stopping for > 15 days at least once)

RESULTS (continued)

Iron Chelation

- Four studies reported iron chelation use (**Table 3**). In two studies from Turkey, where 33% and 38% of patients received transfusions, 22% (Gurkan, 2021[33]) and 26% (Aydin, 2021[16]), respectively, of all patients received iron chelation. In a study from Germany in which ~20% received red cell transfusions (of which 2% received exchange transfusions), 5% of the entire cohort received iron chelation (Kunz, 2021).[38] Finally, 2% of SCD patients in a large study from Saudi Arabia received iron chelation; the proportion receiving transfusions was not reported (Ezzat, 2022).[30]

Table 3. Iron Chelation Use

Author, Year	Country	Data Collection Dates	Patient Number, n	Follow-up Period	Transfusion, %	Iron Chelation Among Entire Cohort, %
Ezzat, 2022[30]	Saudi Arabia	2019 to 2021	22,956	NR	NR	2%
Aydin, 2021[16]	Turkey	Apr 2018 to Apr 2019	53	NR	38%	26%
Gurkan, 2021[33]	Turkey	NR	656	NR	33%	22%
Kunz, 2021[38]	Germany	2011 to 2019	3,200	7 years	~20%/year	5%

Opioids

- Nine studies reported opioid use; the percentage of SCD patients who used opioids ranged from 9.7% (Marfo, 2023)[41] to 100% (Tsouana, 2020).[70] In the five studies that followed patients for ≥1 year, opioid use ranged from 9.7% (Marfo, 2023)[41] to 95% (Silva-Pinto, 2022).[64] Among patients experiencing acute chest syndrome or pain crises, opioids were prescribed to 33% (Munaretto, 2023)[44] to 100% (Tsouana, 2020)[70] of patients.

Novel Disease-modifying Treatments

No studies were identified that described treatment patterns associated with voxelotor or L-glutamine in the regions of interest, while crizanlizumab was identified in three studies:

- Asemissen, 2023[14] (Germany) reported that five of 61 non-HbSC SCD patients in a single-center study used crizanlizumab.
- Silva-Pinto, 2022[64] (Brazil, Italy, Spain, Israel) described patients from a managed access program for crizanlizumab and reported treatment patterns for other SCD therapies.
- Wambacq, 2021[74] (Belgium) reported that eight of the 646 patients in an SCD registry received crizanlizumab.

Published Systematic Reviews

- Five SLRs were identified, which found that strategies to improve adherence were not well understood,[73] particularly in low-resource settings.[60] In higher-resource settings, opioids were typically used to manage acute pain events.[51] The explicit rationale for specific iron chelation combination therapies was not usually provided in the literature.[37] Finally, one review found that hydroxyurea was the mainstay of treatment in the EMR region.[15]

Limitations of the Review

- All studies included in this review were observational in nature, which were heterogeneous in terms of their designs, patient populations, and potential confounding factors. A high proportion of studies were cross-sectional design, which limits the information on treatment patterns to the time of evaluation without subsequent changes over the course of the disease. It is important to consider key characteristics of patients that may influence results, such as age, SCD genotype, and treatment(s) received, as well as health care access, when comparing findings across these studies. Availability of evidence of interest, particularly for non-hydroxyurea treatments, was also limited.

CONCLUSIONS

- **SCD is a severe genetic condition requiring lifelong, tailored treatments.**
- **Patient adherence and persistence for hydroxyurea, the main treatment for SCD, is not well understood. The usage of and adherence to novel disease-modifying therapies (e.g., L-glutamine, voxelotor, and crizanlizumab) is also not well characterized.**
- **Existing limited evidence on treatment patterns in regions with high SCD prevalence indicates substantial care gaps across geographies.**
- **There is a need for robust long-term RWE studies to describe treatment sequences, preferences, and care needs across life stages as well as health outcomes associated with the different treatment strategies.**

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Acknowledgments

This study was sponsored by Pfizer. Editorial support was provided by Richard Leason and Hannah Floyd of Evidera, Inc, and funded by Pfizer, Inc. The team would like to thank Diana Stan for supporting this review.

Disclosures

SR and **PZ** have received research funding from Pfizer. **AF, RW, GTB**, and **MH** are employed by and hold stock options for Pfizer.

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Presented at the ISPOR Europe Conference, 17–20 November 2024, Barcelona, Spain

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