Economic Outcomes and Real-World Adherence of Patients With Sickle Cell Disease With Recurrent Vaso-Occlusive Crises Treated With L-glutamine, Voxelotor, or Crizanlizumab in the United States

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BACKGROUND

- Sickle cell disease (SCD) is a rare genetic disorder characterized by expression of abnormal sickle hemoglobin, which leads to a variety of acute and chronic complications.[1–4]
- Vaso-occlusive crises (VOCs), a hallmark clinical feature in patients with SCD, cause debilitating pain and can lead to additional organ complications and increased mortality; individuals with SCD with recurrent VOCs (defined as ≥ 2 VOCs/year for 2 consecutive years) have increased clinical and economic burden associated with disease.[1–5]
- Standard of care for patients with SCD with recurrent VOCs has long been hydroxyurea and red blood cell transfusions (RBCTs) in addition to supportive care.
- Three chronic therapies were recently approved by United States (US) regulators for the treatment of patients with SCD: L-glutamine (2017), voxelotor (2019), and crizanlizumab (2019).[6–8]
  - L-glutamine is an amino acid indicated to reduce the acute complications of SCD in patients 5 years of age and older.
  - Voxelotor is a hemoglobin S polymerization inhibitor indicated for the treatment of SCD in patients 4 years of age and older; voxelotor is approved under accelerated approval based on increase in hemoglobin.
  - Crizanlizumab is a P-selectin blocker indicated to reduce the frequency of VOCs in patients aged 16 years and older with SCD.
- There is limited data on the real-world economic outcomes of patients with SCD with recurrent VOCs treated with these recently approved chronic therapies in the US.

OBJECTIVES

- To describe economic outcomes of patients with SCD with recurrent VOCs treated with either L-glutamine, voxelotor, or crizanlizumab in the US.

METHODS

Study Design and Database

- A retrospective, pre-post study design using data in the Merative! MarketScan® Research Databases between January 1, 2015 and September 30, 2022 identified patients with SCD with recurrent VOCs who received L-glutamine, voxelotor, or crizanlizumab.
- The MarketScan Databases contain de-identified inpatient medical, outpatient medical, and outpatient prescription drug data for ~228.2 million commercially insured individuals and their dependents between 1995 and 2022, ~15.7 million Medicare enrollees between 1995 and 2022, and ~55.5 million Medicaid enrollees between 1999 and 2022.

Patient Identification

- Patients were included in the analysis if they met the following key inclusion criteria:
  1. ≥1 inpatient or ≥2 outpatient claims with a diagnosis of SCD between January 1, 2015 and September 30, 2022
  2. ≥2 VOC events per year during any 2 consecutive years after the first qualifying SCD diagnosis
  3. ≥ 1 claim for L-glutamine, voxelotor, or crizanlizumab; the date of the first chronic therapy claim is the index date.
  4. ≥12 months of continuous enrollment before and after the index date
- Patients were excluded if they met the following exclusion criteria:
  - Evidence of hematopoietic stem cell transplant or sickle cell trait at any point in the study period
- All patients were assessed in the one year prior to the index date (baseline) and the one year following the index date (follow-up).

Study Measures and Analysis

- Descriptive analyses were conducted for patients with SCD with recurrent VOCs who received L-glutamine, voxelotor, or crizanlizumab.
  - Mean (standard deviation [SD]) values were reported for continuous variables and frequencies/proportions (n, %) for categorical variables.
- Demographics including age, sex, and payer type were assessed at the index date.
- VOCs, healthcare resource utilization (HCRU), and healthcare costs were summarized during the 12 months before and after the index date.
- Healthcare costs, comprised of inpatient, outpatient medical, and outpatient prescription costs, were based on the paid amounts of adjudicated claims, including payer and health plan payments, as well as patient cost-sharing in the form of co-payment, deductible, and co-insurance.
  - Costs were inflated to 2022 US Dollars using the Medical Care Component of the Consumer Price Index.
- Proportion of days covered (PDC) for the index recently approved chronic therapy (i.e., the first chronic therapy a patient received) was measured during the 12-month follow-up period.
- Comparative pre-post analyses were conducted for HCRU and costs using paired *t*-tests; *P*<0.05 was considered statistically significant.

Subgroup Analysis

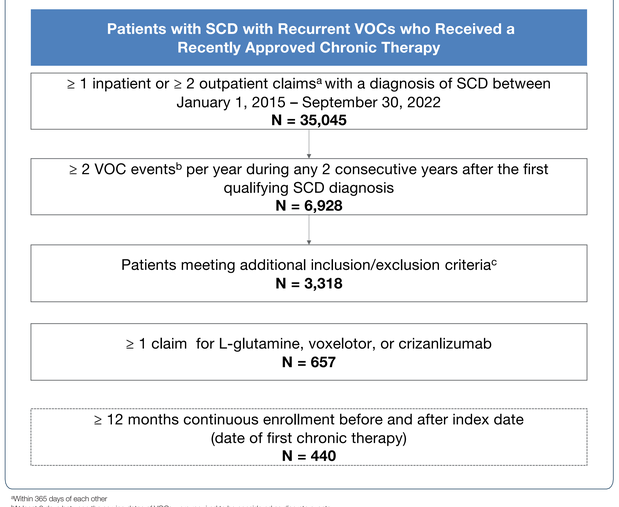
- A subgroup analysis was conducted for healthcare costs based on mean PDC in the 12-month follow-up period.
  - PDC: ≤0.2, >0.20 and ≤0.50, >0.50 and <0.80, ≥0.80

RESULTS

Patient Demographics

- In total, 440 patients initiated a recently approved chronic therapy (L-glutamine: 254; voxelotor: 110; crizanlizumab: 76) and met inclusion criteria (**Figure 1**).
- Mean age of patients with SCD with recurrent VOCs who received a chronic therapy was 23.4 years (SD, range; 11.4, 4-62; **Table 1**).
  - Age ranges (years) for L-glutamine (4-62), voxelotor (11-62), and crizanlizumab (14-58) were broadly aligned to their respective FDA label indication statements[6-8]
- The majority (82.5%) of patients included in the study were captured in the Medicaid database

Figure 1. Patient Selection



[a]Within 365 days of each other
[b]At least 3 days between the service dates of VOCs were required to be considered as discrete events
[c]Additional inclusion/exclusion criteria includes no evidence of sickle cell trait, no evidence of hematopoietic stem cell transplant, and ≥12 months of continuous enrollment before and after the 2nd VOC in the second consecutive year
Abbreviations: HSCT: hematopoietic stem cell transplant

Table 1. Patient Demographics

	Patients with SCD with recently approved chronic therapies (N = 440)
Age, mean (SD, min-max), years	23.4 (11.4, 4-62)
Sex, n (%)	
Female	245 (55.7)
Male	195 (44.3)
Payer Type, n (%)	
Commercial	77 (17.5)
Medicaid	363 (82.5)
Medicaid fee for service (FFS)	223 (50.7)

VOCs and Adherence

- Mean (SD) number of VOCs in the follow-up (7.27 [9.85]) and baseline periods (7.21 [8.82]) were similar for all patients initiating a recently approved chronic therapy (n = 440).
- Mean PDC (SD) for all index therapies (L-glutamine, voxelotor, and crizanlizumab) was 0.37 (0.29).

HCRU and Costs

- There was a statistically significant increase in total number of days of hospitalization and number of outpatient prescriptions in the 12-month follow up period compared to the 12-month baseline period (**Table 2**).
- Mean total costs (SD) increased by $38,111 during the 12-month follow-up period (follow-up: $118,235 [$177,125]; baseline: $80,125 [$120,950]; *P*<0.001; **Figure 2**).
  - Outpatient medical and outpatient pharmacy costs were significantly higher in the follow-up period compared to the baseline period.
- Most of the increased costs ($27,108 [71.1%]) were a direct result of recently approved chronic therapies.
  - Increased costs due to L-glutamine and voxelotor are captured as part of the increased outpatient pharmacy costs, while increased costs due to crizanlizumab are captured primarily in the outpatient costs category.
- The difference in mean healthcare costs between the 12-month follow-up and 12-month baseline period increased as patient adherence to index therapy increased (PDC ≤0.2: $27,666; PDC >0.20 to ≤0.50: $28,404; PDC >0.50 to <0.80: $52,339; PDC ≥0.80: $78,249; **Figure 3**).

Table 2. Healthcare Resource Utilization

	12-month baseline	12-month follow up	Difference
Inpatient			
Number of inpatient admissions, mean (SD)	4.1 (4.2)	4.2 (4.8)	0.1
Total days of hospitalization, mean (SD)	22.4 (30.4)	25.0 (34.7)	2.6*
Outpatient			
Total number of outpatient visits, mean (SD)[a]	62.2 (56.5)	66.2 (72.2)	4.0
Number of emergency room visits, mean (SD)	5.9 (12.9)	5.8 (16.0)	-0.1
Number of office visits, mean (SD)[b]	15.3 (11.3)	15.3 (12.5)	0.0
Number of laboratory visits, mean (SD)[c]	12.6 (12.7)	12.3 (15.4)	-0.2
Number of other outpatient visits, mean (SD)[d]	28.4 (38.7)	32.8 (51.8)	4.3*
Outpatient pharmacy			
Number of prescriptions, mean (SD)	48.6 (35.0)	54.5 (38.0)	5.9*

*P<0.05
[a]Outpatient visit: denoted as a patient, seeing a distinct provider type (e.g., primary care, podiatrist, etc), on a distinct date. Emergency room, outpatient office visits, laboratory visits, and other outpatient visits are included in this total.
[b]Outpatient office visit: denoted as a patient visiting an office setting, at a unique provider type, on a distinct date (e.g., visits usually associated with being evaluated/managed by a physician).
[c]Laboratory visit: denoted as a patient visiting a lab setting, at a unique provider type, on a unique date.
[d]Other outpatient visit: denoted as a patient visiting a non-office outpatient setting, at a unique provider type, on a unique date (e.g., visits for screening, x-ray, transfusions, IV iron chelation administration, etc).

Figure 2. Healthcare Costs

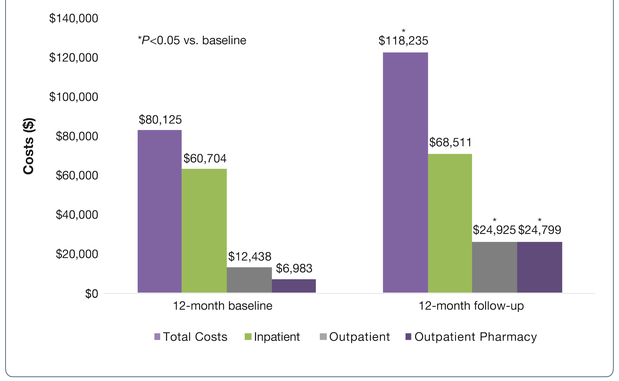
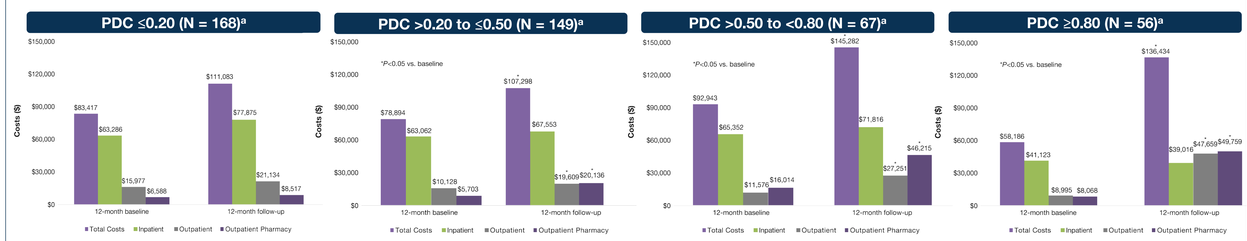


Figure 3. Healthcare Costs by Adherence Level



[a]PDC (proportion of days covered; i.e., adherence) was calculated for the index recently approved chronic therapy.

LIMITATIONS

- Administrative claims data are collected for reimbursement purposes and are therefore subject to potential misclassification.
- Reported costs include insurer paid amounts and patient cost-sharing; the full cost of care to the healthcare system may not be represented, and indirect costs of SCD were not evaluated.
- Individuals who died, went on long-term disability, or otherwise did not meet enrollment criteria may have systematically different outcomes than patients who met enrollment criteria.
- This results may not be fully generalizable to patients with SCD without recurrent VOCs who receive L-glutamine, voxelotor, or crizanlizumab.
- Given limited sample sizes, all three recently approved chronic therapies were analyzed collectively to assess total healthcare costs; each therapy has a unique mechanism of action and FDA labeled indication statement and outcomes may vary by therapy.
- Some indicated benefits of these therapies (e.g., voxelotor's ability to increase hemoglobin levels) are not captured by administrative claims.

CONCLUSIONS

- Although not all recently approved chronic therapies are indicated for VOC reduction, patients experiencing recurrent VOCs who received these therapies had low adherence and continued to experience frequent VOCs and high healthcare costs.
- Total healthcare costs increased by nearly 50% in patients after initiation of recently approved chronic therapies driven by increased costs of the recently approved chronic therapies.
- These results highlight the need for improved treatment options for this population that could reduce disease-related healthcare costs for patients with SCD with recurrent VOCs.

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AUTHOR DISCLOSURES

CU, NL, and SJ are employees of Vertex Pharmaceuticals and may own stock or stock options in the company. MJ and KE are employees of Merative.

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