RESEARCH LETTER

blood advances

TO THE EDITOR:

The use of FDA-approved medications for preventing vaso-occlusive events in sickle cell disease

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Sickle cell disease (SCD) is a chronic disease affecting people across their lifespans. Individuals with SCD face life-threatening complications, including vaso-occlusive pain episodes and chronic end-organ damage. Although SCD affects about 110 000 Americans, health care costs for this population are about $3 billion per year or $30 000 per person.[1,2]

Hydroxyurea has been the only Food and Drug Administration (FDA)-approved treatment for SCD from 1998 to 2017 and 3 new medications for SCD were approved by the FDA since 2017. Although clinical trials have shown fewer acute vaso-occlusive pain episodes using L-glutamine[3] and crizanlizumab[4] and increases in the hemoglobin level using voxelotor,[5] the use of these medications in the real world is unknown. All adults with sickle cell anemia should at least be offered treatment with hydroxyurea[6]; furthermore, up to 63% of individuals with SCD have at least 1 vaso-occlusive pain episode in a year,[7] making them eligible for crizanlizumab, L-glutamine or both. However, in other claims-analyses data, hydroxyurea prescription comprised only 25%,[7,8] and there is a lack of information about using the newer FDA-approved medications.

The use of hydroxyurea, L-glutamine, and crizanlizumab could vary by geographic location owing to the accessibility of the centers to administer infusion drugs like crizanlizumab, and limited access to comprehensive sickle cell care because the use of all the 3 treatments combined is lower after the transition from pediatric to adult health care.[9,10] The use of these therapies may be higher in males owing to concerns about teratogenic effects.[11] We used MarketScan, a claims database, to test the hypotheses that the use of FDA-approved medications would differ by age, sex, and geographic location.

Individuals were identified from 2016 to 2020 through IBM Watson MarketScan administrative billing databases (supplemental Methods). These data include inpatient, outpatient, and emergency department encounters with diagnosis and procedure codes and prescription data. Individuals were included in the study if they had 3 encounters with a diagnosis of SCD, using International Classification of Diseases, Tenth edition (ICD-10) codes similar to existing validated algorithms,[12] and a minimum of 1 year of continuous enrollment during the study period.

The primary outcomes of this study were the uses of hydroxyurea, L-glutamine, voxelotor, and crizanlizumab, either alone or concurrently. Given that these medications were FDA-approved at various times, their study duration differs as follows: hydroxyurea, 2016 to 2020; L-glutamine, 2017 to 2020; voxelotor and crizanlizumab, 2019 to 2020; any medication, 2016 to 2020. Concurrent medication use was defined as a patient being prescribed 2 medications or more of hydroxyurea, L-glutamine, and crizanlizumab. The following independent variables were included: age at first encounter, sex, census bureau region of residence, super rurality, and the Charlson Comorbidity Index. Super rurality was defined as not living within a metropolitan statistical area that incorporated >80% of the US population. Pain episodes were identified using ICD-10 codes from a previous algorithm.[13] The Charlson

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The full-text version of this article contains a data supplement.

Comorbidity Index was constructed using a previously validated list of ICD-9/10 codes and their corresponding weights.[14]

Descriptive statistics were presented as median (interquartile range) for continuous variables and frequency (n [%]) for categorical variables. For each medication, individuals were included if they had 180 days of continuous enrollment following the medication's FDA approval. Logistic regression models were constructed to evaluate the individual-level characteristics independently associated with receiving 1 of the FDA-approved medications for individuals with 2 vaso-occlusive pain episodes on average for every 12 months, similar to the inclusion criteria of the L-glutamine and crizanlizumab trials.[3,4] First, because all medications are FDA-approved for adults, we evaluated all individuals' characteristics in adults aged >18 years. For each model, a log (enrollment time for medication-specific timeframe) offset was included to account for the duration of study follow-up since the medication was approved by the FDA. Confidence intervals were calculated using alpha = 0.05 for primary analysis and sensitivity analysis, with alpha = 0.01 (0.05/5) accounting for the 5 multivariable models used.

The institutional review board determined that this study does not meet the federal definition of human subjects research, and it was therefore exempt from review.

A total of 7957 individuals aged 18 years or older with SCD were included in this study. The median age was 37 years (interquartile range, 26-49), 61.2% (n = 4873) were female, 16.0% (n = 1269) were classified as super-rural, and 57.0% (n = 4531) had on average 2 or more pain episodes annually. Table 1 summarizes unadjusted rates of medication use for the entire population and those with 2 or more pain episodes annually.

Factors associated with medication use varied significantly (Table 2). Notably, for every 10-year increase in age, patients had decreased odds of using hydroxyurea, L-glutamine, and crizanlizumab. Women had increased odds (OR, 1.27; 95% CI, 1.21-1.32) of hydroxyurea use but not for other medications. Individuals with a higher Charlson Comorbidity Index had increased odds of using all the medications. Geographic region variation was noted for hydroxyurea and L-glutamine. Unlike other medications included in this study, not being located in a super-rural geographic location was associated with ~3 times higher odds (OR, 2.93; 95% CI, 1.16-7.42) of using crizanlizumab. Sensitivity analysis revealed similar findings (supplemental Table 1).

Table 1. FDA-approved medication use for all individuals with SCD and those with an average of 2 or more pain episodes in every 12-month period

Medication	All individuals with SCD	Individuals with SCD and 2 or more pain episodes in a year
Hydroxyurea	24.6% (n = 1957/7957)	31.5% (n = 1428/4531)
L-glutamine	2.0% (n = 149/7345)	3.2% (n = 135/4191)
Voxelotor	1.9% (n = 101/5304)	2.9% (n = 85/2888)
Crizanlizumab	1.4% (n = 72/5304)	2.3% (n = 65/2888)
Hydroxyurea + L-glutamine	1.2% (n = 86/7345)	1.8% (n = 76/4191)
Hydroxyurea + Voxelotor	1.0%(n = 55/5304)	1.6% (n = 46/2888)
Hydroxyurea + crizanlizumab	0.6% (n = 34/5304)	1.1% (n = 33/2888)
Crizanlizumab + L-glutamine	0.1% (n = 5/5304)	0.2% (n = 5/2888)
Hydroxyurea + L-glutamine + crizanlizumab	<0.1% (n = 3/5304)	0.1% (n = 3/2888)

Denominators are based on eligible participants when medications were approved by the FDA.

Recently, 2 new medications (crizanlizumab and L-glutamine) have been approved by the FDA to decrease vaso-occlusive events for SCD, adding to a total of 3 approved agents for this indication. Prescription use by age group or geographical region in people with SCD is unknown. In a claims database, we observed that although hydroxyurea continues to be the most prominently prescribed medication (31.5%), followed by L-glutamine (3.2%) and crizanlizumab (2.3% for vaso-occlusive pain), fewer patients received combination therapy. Voxelotor is only approved for those with lower hemoglobin levels and was prescribed to 2.9% of the population. The use of hydroxyurea in individuals with SCD who were privately insured, was comparable with reports of those who were publicly insured (25%-30%).[7,8] Besides these findings, to our knowledge, these data are the first to report the use of new therapies using an administrative data set from nationwide private insurance companies.

Older patients and those who lived in rural areas had significantly lower use of medications approved for vaso-occlusive pain episodes in SCD. Other studies have shown that fewer adults obtain hydroxyurea prescriptions than children, especially after pediatric to adult health care transition.[9,10] These 2 studies used Medicaid databases, but our data demonstrated similar findings with commercial insurance. Crizanlizumab was the only drug significantly less prescribed in super-rural areas, which comprised almost 20% of the population. Crizanlizumab is typically given at infusion centers, leading to access issues for the rural community. Additional possible reasons for lower use have been presented in supplemental Table 2. Further research to understand and overcome access issues of newer therapies related to age and the geographical location will be essential.

Any combination therapy to decrease vaso-occlusive pain was used in ~3% of the population, yet combinations of newer therapies were only used in 0.3%. Barriers should be identified and systematically addressed to improve prescription rates that decrease vaso-occlusive pain events in SCD. In addition to health care access, clinical research must address the knowledge gap of which combination therapy, if any, reduces the incidence rate of vaso-occlusive pain episodes compared with hydroxyurea therapy alone and evaluate the cost-effectiveness of combination therapy. Potential limitations are expected in administrative data sets and are presented in supplemental Table 3.

As the landscape of SCD treatments changes, describing the use of newly-approved FDA therapies to prevent vaso-occlusive pain events and understanding barriers to use, including geographical access, is critical to decreasing preventable SCD-related morbidity. Further studies are needed to identify the obstacles and improve access to FDA-approved medications for SCD in clinical practice.

Table 2. Multivariable logistic regression comparing the use of the FDA-approved medications with demographic and clinical variables in adults aged 18 years and older and those with 2 or more pain episodes on average in every 12-month period

	Comparison	Reference	Hydroxyurea	L-glutamine	Voxelotor	Crizanlizumab	Any medication
Age (y)	10-y increase		**0.63 (0.60-0.67)**	**0.74 (0.64-0.85)**	0.90 (0.77-1.07)	**0.76 (0.63-0.93)**	**0.63 (0.59-0.67)**
Charlson Comorbidity Index	1-unit increase		**1.27 (1.21-1.32)**	**1.19 (1.09-1.31)**	**1.23 (1.11-1.37)**	**1.28 (1.14-1.44)**	**1.30 (1.23-1.42)**
Sex	Female	Male	**1.27 (1.10-1.45)**	0.99 (0.70-1.43)	0.63 (0.39-1.03)	0.76 (0.45-1.30)	**1.20 (1.01-1.42)**
Region	North Central	Northeast	1.11 (0.88-1.41)	**0.38 (0.19-0.76)**	0.68 (0.27-1.68)	1.34 (0.50-3.63)	0.93 (0.70-1.25)
	South		**1.32 (1.11-1.58)**	0.70 (0.47-1.04)	1.40 (0.78-2.51)	**2.40 (1.12-5.14)**	**1.26 (1.02-1.56)**
	West		1.51 (1.08-2.11)	0.98 (0.46-2.09)	2.01 (0.76-5.34)	1.10 (0.23-5.28)	1.05 (0.68-1.61)
Super-rural	No	Yes	0.93 (0.78-1.12)	1.36 (0.81-2.27)	0.92 (0.53-1.60)	**2.93 (1.16-7.42)**	0.96 (0.77-1.20)

Bolded OR and 95% confidence intervals are significant for $P < .05$.

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