Hydroxyurea adherence and associated outcomes among Medicaid enrollees with sickle cell disease

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While laboratory and clinical benefits of hydroxyurea for patients with sickle cell disease (SCD) are well-established, few data describe the extent and implications of non-adherence. We sought to assess adherence to hydroxyurea among patients with SCD and investigate associations between adherence and clinical and economic outcomes. Insurance claims of North Carolina Medicaid enrollees (6/2000-8/2008) with SCD were analyzed. Inclusion criteria included age <65 years, continuous Medicaid enrollment ≥12 months before and following hydroxyurea initiation, and ≥2 hydroxyurea prescriptions. Three hundred twelve patients, mean age 21 (±12.2) years, met inclusion criteria and 35% were adherent, defined as a medication possession ration (MPR) ≥ 0.80; mean MPR was 0.60. In the 12 months following hydroxyurea initiation, adherence was associated with reduced risk of SCD-related hospitalization (hazard ratio [HR] = 0.65, $p = .0351$), all-cause and SCD-related emergency department visit (HR = 0.72, $p = .0388$; HR = 0.58, $p = .0079$, respectively), and vaso-occlusive event (HR = 0.66, $p = .0130$). Adherence was associated with reductions in health care costs such as all-cause and SCD-related inpatient (−$5,286, $p < .0001$; −$4,403, $p < .0001$, respectively), ancillary care (−$1,336, $p < .0001$; −$836, $p < .0001$, respectively), vaso-occlusive event-related (−$5,793, $p < .0001$), and total costs (−$6,529, $p < .0001$; −$5,329, $p < .0001$, respectively). Adherence to hydroxyurea among SCD patients appears suboptimal and better adherence is associated with improved clinical and economic outcomes. Am. J. Hematol. 86:273–277, 2011. © 2010 Wiley-Liss, Inc.

Introduction

Hydroxyurea is currently the only United States Food and Drug Administration (FDA)-approved treatment for severely affected adults with sickle cell disease (SCD). Approved by the FDA in 1998, hydroxyurea has proven laboratory and clinical efficacy for persons with SCD, primarily by increasing the percentage of fetal hemoglobin [1]. Increased levels of fetal hemoglobin help to prevent intracellular sickling, which then reduces hemolysis and vaso-occlusion. The randomized, placebo-controlled multicenter study of hydroxyurea (MSH) demonstrated a significant reduction in the frequency of vaso-occlusive events, acute chest syndrome, hospitalizations, and blood transfusions in hydroxyurea-treated adults with SCD [2]. Beneficial effects of hydroxyurea have also been demonstrated in pediatric patients, albeit primarily in observational studies [3]. Hydroxyurea treatment was also associated with lower mortality in both the MSH cohort and a recently published large study of adults with SCD in Greece [4,5].

Although established as a valuable therapeutic agent, research suggests that hydroxyurea is underutilized in actual clinical practice for patients with SCD [6,7]. A National Institutes of Health (NIH) Consensus Development Conference identified a number of barriers at patient, caregiver, provider, and system-wide levels [8]. In a survey of nearly 350 practitioners who treat patients with SCD, approximately two-thirds reported that adherence was a "very important" concern when treating with hydroxyurea [6]. A more recent survey of 220 pediatric hematologists who care for patients with SCD revealed that the most common factors identified as barriers to prescribing hydroxyurea involved compliance, with >80% acknowledging concern with medication compliance, laboratory monitoring compliance, and contraception compliance in females [9]. However, these studies report provider opinions regarding adherence rather than patient-level data. Even when examining hydroxyurea users, early reports suggest that adherence may be suboptimal [10]. Studies in other chronic diseases demonstrate that medication nonadherence not only reduces treatment benefits but is also associated with poorer clinical outcomes and increased health care utilization and costs [11,12].

The objectives of this study were to use North Carolina Medicaid claims data to document rates of treatment adherence among a hydroxyurea-using cohort of pediatric and adult SCD patients and to investigate the relationships among hydroxyurea adherence, health care utilization, and health care costs.

Methods

This retrospective, longitudinal study was conducted using patient data from the North Carolina Medicaid program, which provides complete coverage to all enrollees who maintain eligibility, including complete provision of prescription benefits. Data for this study were extracted from the database for the period June 2000 through August

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2008. All explicit patient identifiers were removed from the raw data before being released by the data provider, the North Carolina Department of Health and Human Services, Division of Medical Assistance. The Ohio State University's Institutional Review Board determined that this study met all criteria for exemption.

Subjects with ≥2 medical claims with a primary or nonprimary diagnosis of SCD and evidence of hydroxyurea use were initially selected for study inclusion. A diagnosis consistent with SCD was identified as International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes 282.6 and 282.60–282.69. Pharmacy claims for hydroxyurea were identified using relevant national drug codes and healthcare common procedure coding system codes recorded on the claims records. An index date for hydroxyurea treatment was designated as the date of the first prescription claim for hydroxyurea. Only patients with continuous Medicaid enrollment ≥12 months before and following the index date and ≥1 hydroxyurea prescriptions (beyond the initially observed prescription) in the 12 months following the index date were included in the analysis. Because hydroxyurea is also approved for the treatment of chronic myelogenous leukemia, polycythemia vera, and essential thrombocythemia, subjects with these acquired myeloproliferative conditions were excluded. Additionally, patients who were ≥65 years at any point during the observation period were excluded, as were those explicitly listed as being a dual beneficiary (i.e., both Medicare and Medicaid coverage). The reason for these exclusions was that subjects with coverage under both plans would likely have incomplete claims history in the data recorded for each plan, and as such, certain events may not have been reflected in their Medicaid claims record.

Documented patient characteristics included gender and age at the patient's index date. Also documented was the overall underlying comorbidity burden during the 12-month period before the index date, measured using the Charlson comorbidity index score [13]. The number of office visits during the baseline period, defined as the 12 months before the hydroxyurea treatment index date, was used as a proxy for access to care and past healthcare utilization [14].

Adherence to hydroxyurea therapy was measured using the medication possession ratio (MPR), defined as the sum of days supplied with hydroxyurea during the 12 months following initiation, divided by the number of days in the follow-up period (365), less the number of days hospitalized [15]. The data used for this study do not provide details on medications provided during a hospital stay. We have assumed that patients receive a full supply of their medications during a hospital stay and are perfectly adherent during the stay. Thus, we subtract the number of days a patient was hospitalized during the observation period from the denominator of the MPR calculation. Although no consensus exists regarding an appropriate threshold for defining adherence to hydroxyurea, we defined adherence as an MPR ≥0.80 (or 80%), consistent with previously published studies of medication adherence [16,17]. Because the calculations necessary for the MPR require the number of days supplied by a prescription, patients with any hydroxyurea prescription for which this information was missing were excluded from analysis.

SCD-related complications were defined as the occurrence of a diagnosis for vaso-occlusive event (ICD-9-CM diagnosis codes 282.62, 282.64, and 282.69), gallstones (ICD-9-CM 574.xx), avascular necrosis (ICD-9-CM 733.4), stroke (ICD-9-CM 430.xx, 431.xx, 432.xx, 433.01, 433.11, 433.21, 433.31, 433.41, 433.51, 433.61, 433.71, 433.81, 433.91, and 434.xx), or acute chest syndrome (ICD-9-CM 517.3). For each study group (i.e., hydroxyurea adherent and nonadherent), the number of SCD-related complications in the 1-year postindex date period was calculated and reported.

Total all-cause and SCD-related health care utilization and costs were assessed separately for hydroxyurea adherent and nonadherent patients. Resource utilization and costs were separated according to care setting (i.e., inpatient, emergency department, physician office visit, ancillary care, and pharmacy) in which they occurred based on place of service codes, charge descriptions, and other descriptive information available on each claim. SCD-related encounters and associated costs were defined based on claims for medical services in which SCD was recorded as the primary diagnosis. SCD-related pharmacy utilization and costs were defined as prescriptions obtained and costs incurred for hydroxyurea. Additionally, the costs for all opiate prescriptions filled in the 12 months following hydroxyurea initiation were assessed. All cost data were inflated to 2008 dollars.

The statistical significance of descriptive differences in the outcomes of interest between those adherent and nonadherent to hydroxyurea therapy was measured using *t*-tests and χ^2 tests. Additionally, multivariable regression models were estimated to control for confounding. The relative risk of complications and associated events was assessed using Cox proportional hazards models, in which time to first complication or event of interest following the index date was estimated as a function of a dichotomous indicator for hydroxyurea adherence and baseline patient characteristics. Baseline characteristics included age at index date, gender, Charlson comorbidity index score, and number of office visits in the 12 months before the index date. Because cost data in insurance claims databases are often skewed, generalized linear models (GLM) models were used to assess the effect of hydroxyurea adherence on health care costs [18]. The same covariates used in the Cox proportional hazards models were used in the GLM models. An added appeal of GLM is that this approach allows for obtaining adjusted, predicted mean costs in the dollar scale for subjects in different groups (in this case, hydroxyurea adherent and nonadherent). Predicted, adjusted mean values were compared between the adherent and nonadherent groups, and statistically significant differences noted. All data management and analyses were performed using SAS® (Version 9) and Stata® (Version 11) statistical software packages.

Results

After applying all study inclusion and exclusion criteria, 312 subjects, out of a total of 5,469 patients with SCD, were included in the study population.

Although there is no consensus regarding clinical indications for hydroxyurea based on high-grade evidence, we did attempt to determine the proportion of all SCD patients (i.e., before imposing any study selection criteria) who met suggested criteria for receiving hydroxyurea therapy (i.e., more than three inpatient stays consistent with a painful SCD event) [19]. Among the 5,469 SCD patients, there were 397 patients who would be recommended for hydroxyurea use per these guidelines, but more than half had not received the drug. Further, among the 603 users, 70% did not appear to meet the NIH's "recommendation" criterion. However, these patients might actually have met this criterion before the start date of the study period. These figures may be conservative because the population from which they were drawn did not mandate continuous enrollment; relevant events may have occurred during a time period in which a patient was unenrolled.

As illustrated in Table I, among the study population, nearly two-thirds (64.7%) were classified as nonadherent (i.e., MPR ≤ 0.8) with their hydroxyurea therapy. The mean MPR (SD) across all patients was 0.60 (0.32); for the adherent group, it was 0.97 (0.06), whereas for the nonadherent, it was 0.39 (0.19). Within the nonadherent group, 24.3% had an MPR less than 0.20 and 81.2% had an MPR less than 0.60. Mean age and the proportion of females were not statistically different between the groups. Charlson comorbidity index scores were low overall, but significantly higher among nonadherent patients ($P = 0.0166$). Nonadherent patients also had significantly more office visits during the 12 months before the hydroxyurea index date ($P = 0.03$). During the 1 year following initiation of hydroxyurea, a greater proportion of nonadherent patients had ≥1 SCD-related inpatient stays, ≥1 emergency department visits (both all-cause and SCD-related), and ≥1 vaso-occlusive events. Similarly, nonadherent patients had significantly greater mean numbers of vaso-occlusive events as well as all-cause and SCD-related hospitalizations. The number of acute chest syndrome, stroke, gallstone, and avascular necrosis events were low overall; some significant differences between groups were found, but these findings should be viewed with caution because of the low number of occurrences of each of these events. Because of the infrequent nature of these events, they were not included in multivariate analysis.

Multivariable regression models further demonstrated that significant benefits may be attributed to hydroxyurea adherence. Cox proportional hazards models revealed that

TABLE I. Characteristics of 312 North Carolina Medicaid Enrollees (June 2000 to August 2008) With Sickle Cell Disease Prescribed Hydroxyurea Therapy, by Adherence Status

	All patients (N = 312)	Adherent (N = 110)	Nonadherent (N = 202)	P-value
Baseline characteristics				
Age at index date, mean (SD)	20.91 (12.23)	20.32 (12.23)	21.24 (12.24)	0.5284
Median (interquartile range) age at index date	18 (12–29)	16 (11–30)	19 (12–29)	
Female, N (%)	152 (48.7%)	47 (42.7%)	105 (52.0%)	0.1182
Charlson comorbidity index score, mean (SD)	0.57 (1.16)	0.35 (0.84)	0.68 (1.29)	0.0166
Preindex period office visits, mean (SD)	15.39 (28.95)	10.58 (28.49)	18.0 (28.94)	0.0303
Median (interquartile range) number of preindex period office visits	5 (1–19.5)	2 (2–26.5)	9 (2–23)	
Events 1 year after initiating hydroxyurea				
Had ≥1 inpatient stays, N (%)	140 (44.9%)	44 (44.0%)	96 (47.5%)	0.2017
Number of inpatient stays, mean (SD)	1.40 (2.47)	0.80 (1.41)	1.72 (2.83)	0.0014
Median (interquartile range) number of inpatient stays	0 (0–2)	0 (0–2)	0 (0–2)	
Had ≥1 SCD-related inpatient stays, N (%)	117 (37.5%)	33 (33.0%)	84 (41.6%)	0.0435
Number of SCD-related inpatient stays, mean (SD)	1.04 (2.04)	0.52 (1.09)	1.32 (2.36)	0.0009
Median (interquartile range) number of SCD-related inpatient stays	0 (0–1)	0 (0–1)	0 (0–2)	
Had ≥1 emergency department visits, N (%)	191 (61.2%)	57 (51.8%)	134 (66.3%)	0.0119
Number of emergency department visits, mean (SD)	2.67 (6.69)	1.95 (6.06)	3.06 (7.00)	0.1639
Median (interquartile range) number of emergency department visits	1 (0–3)	1 (0–2)	1 (0–3)	
Had ≥1 SCD-related emergency department visits, N (%)	128 (41.0%)	33 (30.0%)	95 (47.0%)	0.0035
Number of SCD-related emergency department visits, mean (SD)	1.63 (4.68)	0.93 (2.70)	2.01 (5.43)	0.0506
Median (interquartile range) number of SCD-related emergency department visits	0 (0–1)	0 (0–1)	0 (0–2)	
Had ≥1 vaso-occlusive events, N (%)	175 (56.1%)	52 (47.3%)	123 (60.9%)	0.0206
Number of vaso-occlusive events, mean (SD)	2.60 (5.19)	1.23 (2.37)	3.35 (6.09)	0.0005
Had ≥1 gallstone events, N (%)	10 (3.2%)	7 (6.36%)	3 (1.5%)	0.0371
Number of gallstone events, mean (SD)	0.04 (0.20)	0.07 (0.29)	0.01 (0.12)	0.0151
Had ≥1 stroke events, N (%)	3 (1.0%)	0 (0.0%)	3 (1.5%)	0.5546
Number of stroke events, mean (SD)	0.02 (0.19)	0.00 (0.00)	0.02 (0.23)	0.2656
Had ≥1 avascular necrosis events, N (%)	15 (4.8%)	1 (0.9%)	14 (6.9%)	0.0175
Number of avascular necrosis events, mean (SD)	0.08 (0.40)	0.01 (0.10)	0.12 (0.48)	0.0194
Had ≥1 acute chest syndrome events, N (%)	8 (2.6%)	1 (0.9%)	7 (3.5%)	0.2681
Number of acute chest syndrome events, mean (SD)	0.03 (0.19)	0.01 (0.10)	0.04 (0.22)	0.1662

TABLE II. The Association Between Hydroxyurea Adherence and the Risk of Clinical Events in the 1st Year Following Initiation of Hydroxyurea—Cox Proportional Hazard Regression Results

Event	Hydroxyurea adherence hazard ratio	95% Confidence interval	P-value
All-cause inpatient stay	0.78	0.54–1.11	0.1679
SCD-related inpatient stay	0.65	0.43–0.97	0.0351
All-cause emergency department visit	0.72	0.52–0.98	0.0388
SCD-related emergency department visit	0.58	0.39–0.87	0.0079
Vaso-occlusive event	0.66	0.47–0.92	0.0130

Note: Covariates included in each regression model were: dichotomous indicator for adherent to hydroxyurea therapy, defined as MPR ≥0.80; age at index date; age at index date squared; gender; Charlson comorbidity index score; Charlson comorbidity index score squared; and an access to care proxy, defined as the total number of office visits in the 12 months before the index date.

TABLE III. Predicted, Adjusted Health Care Costs in the 1st Year Following Initiation of Hydroxyurea, by Adherence Status

Service setting	Adherent (N = 110)	Nonadherent (N = 202)	P-value
Inpatient			
All-cause	$4,494	$9,780	<0.0001
SCD-related	$2,912	$7,315	<0.0001
Emergency department			
All-cause	$229	$837	<0.0001
SCD-related	$130	$552	<0.0001
Physician office visit			
All-cause	$6,092	$3,483	0.4560
SCD-related	$1,941	$1,865	0.8890
Ancillary care			
All-cause	$2,575	$3,911	<0.0001
SCD-related	$1,630	$2,466	<0.0001
Pharmacy			
All-cause	$2,742	$2,579	0.4400
Hydroxyurea-costs	$354	$158	<0.0001
Total health care utilization			
All-cause	$13,907	$20,436	<0.0001
SCD-related	$6,768	$12,097	<0.0001

Note: Predicted, adjusted values derived following GLM regressions models for each service setting. Covariates included in each model were: dichotomous indicator for adherent to hydroxyurea therapy, defined as MPR ≥0.80; age at index date; age at index date squared; gender; Charlson comorbidity index score; Charlson comorbidity index score squared; and an access to care proxy, defined as the total number of office visits in the 12 months before the index date.

hydroxyurea adherence was associated with an ~40% reduction in the risk of an SCD-related emergency room visit, a 28% reduction in the risk of any emergency room visit, a 35% reduction in the risk of an SCD-related hospitalization, and a 34% reduction in the risk of a vaso-occlusive event (Table II).

When comparing health care costs between adherent and nonadherent patients, mean predicted, adjusted costs for hospitalizations, emergency room visits, other ancillary care, and total health care costs were higher among nonadherent patients, both all-cause and SCD-related, although SCD-related pharmacy costs were slightly higher in the adherent group (Table III). All-cause inpatient and emergency room costs were greater for the nonadherent group, as were SCD-related inpatient and emergency room costs. Both all-cause and SCD-related ancillary care costs were greater for the nonadherent group. Finally, all-cause and SCD-related total costs were each greater among those nonadherent with hydroxyurea treatment, $20,436 versus $13,907 ($P < 0.0001$) and $12,097 versus $6,768 ($P < 0.0001$). Two additional models not presented in Table III were also estimated. Adjusted vaso-occlusive event-related costs were greater among the nonadherent group than the adherent group ($8,887 versus $3,094, $P < 0.0001$). Lastly, mean predicted, adjusted costs for opiates did not differ significantly between adherent and nonadherent patients ($656 versus $621, $P = 0.7400$).

We did conduct subanalyses for the 159 pediatric hydroxyurea users (0–18 years of age). Nearly 41% (40.8%) of these pediatric patients had an MPR of at least 0.8 and were classified as adherent, as compared with 29.4% of patients >18 years of age ($P = 0.0340$). Cox regression models (data not shown) did not demonstrate a statistically

significant relationship between adherence and the risk of inpatient stay, emergency room visit, or vaso-occlusive event, although the estimated adherence hazard ratios for these models were each <1. However, treatment adherence in the 12 months following hydroxyurea initiation was associated with a significant reduction in both all-cause and SCD-related inpatient, emergency, and total costs. For example, SCD-related costs were $5,772 in adherent patients compared with $8,631 in nonadherent patients ($P < 0.001$).

Discussion

Hydroxyurea is a powerful therapeutic agent with proven laboratory and clinical efficacy for patients with SCD. Our work adds to the body of knowledge regarding the benefits of hydroxyurea by demonstrating that in a "real-world" population of Medicaid patients prescribed hydroxyurea, adherence to this treatment is associated with significantly decreased health care utilization and costs. We found that ~10% of patients with SCD in the North Carolina Medicaid system received hydroxyurea treatment. These findings are similar to those of Tripathi et al., who examined hydroxyurea use in pediatric patients with SCD in the South Carolina Medicaid system [20]. These authors found that 8% of patients were treated with hydroxyurea, and that hydroxyurea was being administered to the most severely ill children, many of whom had already developed organ-specific complications before the institution of hydroxyurea.

In our population of 312 hydroxyurea users, only 35% were considered to be adherent (defined as MPR $\geq$ 0.80) to their therapy, whereas nearly half had an MPR < 0.60 (i.e., poorly adherent). However, our study population demonstrated a greater degree of adherence than that previously reported in a similar study conducted using Florida Medicaid data [10]. Among adherent patients, the mean MPR was almost perfect (0.97), suggesting that adherent patients are likely to be very attentive to their therapies. Efforts to increase medication adherence to hydroxyurea should be developed, potentially using published strategies to improve the health outcomes of treated patients [21]. Adherence is affected not only by patient behaviors but also by the medical system and the competence, nature, and interest of providers. Some providers may not be familiar with the methods of initiating and monitoring therapy with hydroxyurea, and as a result, one solution to improving adherence should include educating the providers caring for patients with SCD.

Adherence to hydroxyurea therapy was associated with reduced risk of inpatient and emergency room encounters as well as vaso-occlusive events as well as reduced inpatient, emergency room, ancillary care, and total health care costs. With respect to SCD-related total costs, our multivariate regression models indicate that adherence to hydroxyurea was associated with a reduction of just more than $5,300, more than offsetting the slight increase in related pharmacy costs (+$196) attributable to adherence to hydroxyurea. It is true that adherent patients may have lower health care costs in general because they are more invested in their health and adopt other healthy behaviors. However, our findings are consistent with research in other chronic diseases demonstrating that medication adherence is associated with reduced health care utilization, costs, and risk of clinical outcomes [11,12]. Further, our findings are similar to a cost-effectiveness study of hydroxyurea based on data from the MSH [22]. In this cost-effectiveness study, Moore et al., applied cost estimates to each unit of resource utilization based on the perspective of a public insurer, and adjusted all costs to 1995 dollars. Comparison of total costs between the hydroxyurea and placebo-treated patients over the 2-year-study period demonstrated a statistically significant difference with a $5,210 increment in means between the two study arms.

As a sensitivity analysis, we lowered the adherence threshold to $\geq$0.60; 48% of patients were then considered adherent. Significant economic benefits (i.e., all-cause and SCD-related inpatient and emergency room costs; SCD-related total costs) of adherence at the $\geq$0.80 threshold were no longer statistically significant using the $\geq$0.60 definition. However, adherence at the lower threshold was still associated with a significant reduced risk of SCD-related emergency room visits and vaso-occlusive events.

Our findings should be interpreted in light of the strengths and limitations of our study design and data source. Because North Carolina has a large African–American population and it is estimated that two-thirds of pediatric and adult patients with SCD are publicly insured [23,24], the use of North Carolina Medicaid claims data provides access to a large population of SCD patients. However, our population may not be representative of the national SCD population. During our study period, one of 10 NIH-funded Comprehensive Sickle Cell Centers was located in North Carolina. Patients with SCD in North Carolina, therefore, may have had greater access to specialty SCD care, may have been more likely to be prescribed hydroxyurea, and perhaps were more likely to be adherent to the therapy. With regard to our study design, tracking pharmacy refills may underestimate adherence if dose reductions occur, or may overestimate adherence when prescriptions are filled but medication is not taken. In a recent prospective study of hydroxyurea therapy among 75 children with SCD, adherence was 49% when defined as 5 or more refills in a 6 month period, but 82–85% when using caregiver visual analog scales, caregiver Modified Morisky scores, or medical provider estimates [25]. Compliance with medical care also affects patient health outcomes and our study design does not allow us to evaluate patient adherence to routine comprehensive SCD clinic visits or hydroxyurea clinic visits.

Our work is also subject to the limitations inherent in any analysis of administrative claims data. Medical conditions (e.g., SCD, vaso-occlusive events) were identified based on ICD-9-CM diagnosis codes that, if recorded inaccurately or not recorded at all, may have caused some patients and events to be misidentified. The validity of the results presented here depends, in part, upon the accuracy of record keeping and reporting among providers submitting claims to the North Carolina Medicaid system. Use of administrative data also does not allow for understanding the causes of nonadherence to hydroxyurea. Although it appears that there are very few, if any, pediatric nonresponders to hydroxyurea, studies in adults demonstrate that 25% or more of hydroxyurea users may not achieve a sustained increase in fetal hemoglobin [1,2,26]. We are unable to identify nonresponders in our study population and how this phenomenon may have impacted adherence.

These cost analyses included only the direct medical costs associated with SCD and ignore additional societal costs that may be associated with this condition, such as the costs of lost workplace productivity (including parental absenteeism due to a sick child), out-of-pocket expenditures, and decreased quality-of-life. Future studies exploring the equally important aspects of indirect SCD-related costs are needed. Both our study and the MSH cost-effectiveness study looked at relatively short time frames. It is quite likely that decreases in the rates of mortality, stroke, and end-organ damage due to hydroxyurea adherence would lead to even greater cost savings, and cost-effectiveness studies of this type are also needed [22].

In conclusion, the results of this research provide the first real-world description of hydroxyurea adherence in a large SCD population. This evaluation of the clinical and eco-

nomic benefits associated with adherence to hydroxyurea is another call to action for clinical practitioners and other healthcare researchers to increase the availability of this agent to eligible children and adults with SCD. The NIH have emphasized the clear need for research to develop "interventions aimed at reducing parent/caregiver, provider, and healthcare system barriers to hydroxyurea treatment [8]." The results of this study highlight the need for further research to explore methods for improving hydroxyurea utilization and adherence rates among patients with SCD who would benefit from treatment.

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