PSY17

Economic Outcomes Associated With Hydroxyurea Adherence Among Pediatric Medicaid Enrollees With Sickle Cell Disease

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BACKGROUND

- Sickle cell disease (SCD) is a genetic disorder affecting 50,000-100,000 people in the United States (US)[1]
- Patients with SCD frequently experience unexpected, intermittent, and often life-threatening complications, leading to emergency room (ER) visits and frequent hospitalizations, each with substantial economic costs
- Hydroxyurea (HU) is the only pharmaceutical product approved for the treatment of SCD
  - HU increases production of fetal hemoglobin-containing red cells and dilutes the number of sickled cells in circulation[2]
  - In clinical trials, HU has been shown to reduce frequency of vaso-occlusive crises[3]
  - Although not approved in the US for use in pediatrics, HU is used in this population[4]
- Treatment nonadherence is widespread in chronic diseases
  - Nonadherence reduces treatment benefits, can bias assessments of treatment effectiveness, and has been associated with poorer disease prognosis[5-9]
  - Higher relapse rates, increased morbidity, additional treatment seeking, and lost workplace productivity have been identified as primary avenues through which nonadherence affects the costs of illness[10,11]
  - This burden has been estimated to be $100 billion per year across all chronic diseases in the US[6]
- Prior research has suggested that adherence to HU is suboptimal[12]

OBJECTIVE

- To assess the extent to which pediatric patients diagnosed with SCD are adherent with HU therapy and the potential association between HU adherence and clinical and economic outcomes

METHODS

- Data were extracted from the North Carolina Medicaid program
  - Data consisted of patient demographics, institutional and professional medical claims for inpatient and outpatient services, outpatient prescription drug claims, and start and stop dates of Medicaid enrollment
  - Each medical claim contained, among other variables, date and place of service (e.g., inpatient, outpatient, ER), amount paid, and up to nine International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes
  - Prescription drug claims included the National Drug Code (NDC), brand and generic name, quantity dispensed, days' supply, strength, and paid amount for prescriptions obtained
- Inclusion/exclusion criteria:
  - ≥ 1 primary or nonprimary diagnosis of SCD (ICD-9-CM codes 282.6 and 282.6x) and ≥ 2 prescription claims for HU between June 1999 and August 2008
  - HU (brand names Hydrea and Droxia) prescriptions were identified using relevant NDCs
  - ≤ 18 years of age on the HU index date
  - Because HU is also indicated for treatment of chronic myelogenous leukemia,polycythemia vera, and essential thrombocythemia, patients with evidence of any of these conditions were excluded
- An index date was defined for each patient as the date of the first observed HU prescription claim
- Patients were required to have:
  - ≥ 12 months of continuous Medicaid enrollment prior to their index date with no evidence of an HU prescription to help ensure that the index date was a reasonable marker for HU initiation
  - ≥ 12 months of continuous enrollment following their index date to ensure an adequate follow-up period over which outcomes could be evaluated
- Adherence was measured using the medication possession ratio (MPR)
  - MPR = Sum of days HU was supplied in observation period ÷ (Days in observation period, less days spent in the hospital)
  - Subjects with an MPR ≥ 0.80 were classified as adherent
- Patient characteristics measured at the index date and included in subsequent regression models included age, sex, Charlson Comorbidity Index (CCI) score, and number of SCD-related office visits in the year prior to initiating HU
  - CCI score assessed overall morbidity
  - Number of office visits was a proxy for underlying severity of disease and access to care
- Cost data, overall and for distinct care settings (e.g., inpatient, office visit), including pharmaceutical products, were summarized over the follow-up period after HU initiation
- Multivariate regression models were estimated to formally assess the association between overall HU adherence and various outcomes
  - Generalized linear models (GLMs) were estimated to assess the effect of HU adherence on costs for inpatient, office visit, other outpatient and ancillary, and ER care, as well as for pharmaceutical-related and total costs
  - Cox models were estimated to assess the incremental effect of HU adherence on the risk of inpatient and ER encounters, as well as vaso-occlusive events
    - Models estimated included the outcome of interest as a function of a dichotomous indicator for HU adherence (1 = MPR ≥ 0.80, 0 = MPR < 0.80) and additional variables to control for baseline patient characteristics
    - All-cause and SCD-related models were estimated for each outcome

RESULTS

- 159 patients met all study inclusion criteria
- Roughly 40% (n = 65) had an MPR of at least 0.80 and were classified as adherent with HU treatment, leaving a substantial majority (60%) considered to be nonadherent to their HU therapy
  - The mean MPR across all subjects was 0.63
  - Among the study sample (Table 1):
    - More than half (55%) of all subjects were male
    - The mean age among those identified for study inclusion was 11.3 years; among the adherent, the mean age was nearly 12 years
    - Both populations had low CCI scores
    - The nonadherent population had a statistically greater number of pre-index date period SCD-related office visits than the adherent population

Table 1. Characteristics of 159 Pediatric North Carolina Medicaid Enrollees (1999-2008) With Sickle Cell Disease Prescribed HU Therapy, by Adherence Status

Characteristic	All Patients (n = 159)	Adherent (n = 65)	Nonadherent (n = 94)	*P* Value
Age at index date, mean (SD)	11.34 (4.40)	11.74 (4.07)	11.06 (4.62)	0.3437
Female, n (%)	71 (44.7%)	30 (46.2%)	41 (43.6%)	0.7518
CCI Score, mean (SD)	0.43 (0.96)	0.34 (0.83)	0.48 (1.04)	0.3336
Pre-index SCD-related office visits, mean (SD)	10.77 (15.06)	7.26 (11.98)	13.20 (16.49)	0.0140

CCI = Charlson Comorbidity Index; HU = hydroxyurea; SCD = sickle cell disease; SD = standard deviation.

- Although multivariable Cox regression models (Table 2) did not demonstrate a statistically significant relationship between adherence and the risk of inpatient stay, ER visit, or vaso-occlusive event, the hazard ratios for these models were each < 1

Table 2. The Risk of All-Cause and SCD-Related Events In Patients Adherent to HU as Compared With Nonadherent Patients, Cox Proportional Hazard Regression Results

Event	HU Adherence Hazard Ratio	95% CI	*P* Value
All-cause inpatient stay	0.917	0.554-1.518	0.7368
SCD-related inpatient stay	0.725	0.405-1.298	0.2788
All-cause ER visit	0.687	0.441-1.070	0.0971
SCD-related ER visit	0.652	0.351-1.209	0.1743
Vaso-occlusive event	0.723	0.452-1.154	0.1740

CI = confidence interval; ER = emergency room; HU = hydroxyurea; SCD = sickle cell disease; SD = standard deviation.

- Comparing predicted values using multivariate GLM regression models (Table 3) revealed that in the 12 months following HU initiation, treatment adherence was associated with a significant reduction in both all-cause and SCD-related inpatient, ER, other outpatient and ancillary care, and total costs
  - Conversely, adherence was associated with an increase in all-cause and SCD-related pharmacy costs

Table 3. Predicted, Adjusted Health Care Costs in the First Year Following Initiation of HU

Service Setting	Adherent (n = 65)	Nonadherent (n = 94)	*P* Value
Inpatient services			
All-cause	$4,755	$6,750	< 0.0001
SCD-related	$2,925	$4,684	< 0.0001
ER visits			
All-cause	$204	$515	< 0.0001
SCD-related	$109	$324	< 0.0001
Office visits			
All-cause	$1,945	$2,075	0.3230
SCD-related	$1,086	$1,200	0.1050
Other outpatient/ancillary services			
All-cause	$2,162	$3,125	< 0.0001
SCD-related	$1,602	$2,109	0.0060
Pharmacy			
All-cause	$1,246	$1,041	0.0250
SCD-related	$369	$178	< 0.0001
Total health care utilization			
All-cause	$10,140	$13,658	< 0.0001
SCD-related	$5,772	$8,631	< 0.0001

ER = emergency room; HU = hydroxyurea; SCD = sickle cell disease.

DISCUSSION

- Only approximately 40% of pediatric patients with SCD receiving HU were adherent to their therapy (i.e., MPR ≥ 0.80)
- Further, North Carolina Medicaid data suggest that only approximately 50% even had an MPR ≥ 0.60
  - This estimate is nonetheless better than findings from previous research, which suggested that only 30.2% of Medicaid-enrolled SCD patients in Florida had an MPR of 0.60 or better[12]
- Apparent increased adherence may be attributable to:
  - Analyzing slightly more current data, suggesting improved use and understanding of HU
  - Including only pediatric patients in the study sample
  - Presence of a National Heart, Lung, and Blood Institute (NHLBI) Comprehensive Sickle Cell Center in North Carolina, possibly leading to differences in practice patterns
- Adherence with HU was found to significantly reduce costs for a number of health care resource use parameters
  - The slight increase in pharmacy costs associated with adherence was offset by reductions in other costs attributable to adherence

LIMITATIONS

- Medication refill patterns in administrative data, while reflective of real-world prescription dispensing, may not reveal the true intent or directions of the prescribing physician
- The observation of a prescription claim assumed complete ingestion of the medication obtained; it is possible, however, that individuals will dispose of medication prior to refill or stockpile it for future use
- Patients were identified based on ICD-9-CM diagnosis codes which, if recorded inaccurately, may have caused some patients to be misidentified as having SCD
- Data on key clinical parameters such as the severity of crises experienced by patients, which may have a substantial impact on resource utilization and costs, were not available
- These results do not account for indirect costs, such as those due to lost wages or missed work time due to the disease (i.e., parental workplace absenteeism)
- The data for this study were drawn from the North Carolina Medicaid system; therefore, results may not be generalizable to other populations

CONCLUSIONS

- Among pediatric patients with SCD, adherence with HU appears to be suboptimal
- HU adherence does appear to be associated with reduced health care utilization and costs
- Additional research is needed to further explore the relationship between adherence and the risk of clinical and utilization-related events
- Steps should be taken to ensure that patients who would be recommended for HU are receiving it
- Efforts to promote HU adherence may potentially lead to improved health outcomes for Medicaid-enrolled SCD patients and cost savings for the Medicaid system

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