Letters

RESEARCH LETTER

Proportion of Adults With Sickle Cell Anemia and Pain Crises Receiving Hydroxyurea

The recommendation from the 2014 National Heart, Lung, and Blood Institute guidelines1 to treat all adults with sickle cell anemia (SCA) and 3 or more moderate to severe pain crises within 1 year with hydroxyurea was rated as strong based on high-quality evidence reviewed in 2008.2,3 Despite benefits in reducing pain crises, hospitalizations, blood transfusions, and possibly mortality, it is thought that hydroxyurea is underused, although the extent of its use is unknown.2 We sought to document the use of hydroxyurea when indicated for SCA in a large insurance claims database.

Methods | Data were obtained from the deidentified Optum Normative Health Informatics database, a nationwide sample of commercial health and pharmacy claims from more than 36 million residents in all 50 states and Washington, DC.4,5 Compared with the US population, the database has more patients aged 18 to 54 years, 1.3% fewer women, 2.3% fewer blacks, 6.4% fewer Latinos, and 6.8% more whites.

Adults (aged ≥18 years) with 1 or more inpatient or outpatient claims between January 1, 2009, and June 30, 2013, for probable SCA were identified using International Classification of Diseases, Ninth Revision (ICD-9) codes 282.61 (HbSS disease without crisis) or 282.62 (HbSS disease with crisis) on at least 2 encounters. Patients were selected when they had ≥3 or more hospitalizations, emergency department (ED) visits, or both within 12 months that included 1 of the 5 most frequent diagnosis codes used for patients with SCA and pain crises (HbSS disease with crisis [282.62]; acute chest syndrome [517.3]; pain in limb [729.5]; chest pain, unspecified [786.50]; other chest pain [786.59]), independent of existing or continuing treatment with hydroxyurea. Treatment was defined as filling 1 or more hydroxyurea prescriptions during the 3, 6, or 12 months of continued enrollment following the third episode.

The percentage of treated patients, 95% confidence intervals, and χ² for trend were calculated using SAS version 9.3 (SAS Institute Inc). A 2-sided P value of <.05 was considered statistically significant. This analysis was exempted from review by the Western Institutional Review Board.

Results | Of an enrolled population of 26 691 901, we identified 2086 adults with probable SCA (Table). Of these, 677 had at least 3 pain-related hospitalizations or ED visits within 12 months and 570 had at least 3 months of coverage after the third episode. Among them, 86 (15.1%; 95% CI, 12.3%-18.3%) were treated with hydroxyurea within 3 months of their third encounter. The percentage of treated patients increased slightly to 18.2% (95% CI, 15.0%-21.8%) at 6 months and to 22.7% (95% CI, 18.9%-27.0%) at 12 months (P = .002 for trend).

Discussion | Despite evidence demonstrating the benefits of hydroxyurea in patients with SCA and frequent pain crises,2 this analysis suggests that more than 3 of 4 patients who might benefit were not treated with this safe and inexpensive drug. Several barriers to treatment have been identified, including fear of adverse events, lack of clinician training, and failure to engage in shared decision making.2 Our estimate reflects the combined effect of all barriers to treatment, regardless of source.

This analysis was limited by the use of ICD-9 codes to identify patients with SCA, an approach that can lead to missing potentially eligible patients. In addition, because some pain crises may be managed without hospitalizations or ED visits, some patients with 3 or more crises and suitable for hydroxyurea may not have been included. Furthermore, this definition does not take into account the broadened criteria described in new guidelines for the use of hydroxyurea, such as patients who have daily pain that affects their quality of life.1

Our data do not include the large uninsured or publicly insured population who may have more limited access to health care or awareness of treatment options. Therefore, these findings may not be representative of the entire US population with SCA and may be a conservative estimate of the hydroxyurea treatment gap. To address this gap, it may be necessary to enhance patient outreach and clinician training and develop health care quality measures aimed at increasing the use of hydroxyurea for all patients who would benefit.

Table. Characteristics of 2086 Adults With Probable Sickle Cell Anemia (SCA) Reported in a Large Commercial Insurance Database Between January 1, 2009, and June 30, 2013

<table>
<thead>
<tr>
<th>Adults With Probable SCAa</th>
</tr>
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<tbody>
<tr>
<td>Age, median (25th–75th percentile), y</td>
</tr>
<tr>
<td>Female sex</td>
</tr>
<tr>
<td>Duration of continuous enrollment, median (25th–75th percentile), mo</td>
</tr>
<tr>
<td>Filled ≥1 prescription for hydroxyurea during enrollment period</td>
</tr>
<tr>
<td>Average number of emergency visits or hospitalizations for pain per year, median (25th–75th percentile)</td>
</tr>
<tr>
<td>Emergency visit or hospitalization for pain during enrollment period</td>
</tr>
<tr>
<td>≤1</td>
</tr>
<tr>
<td>≥3 over 12 mo</td>
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</table>

* Data are expressed as No. (%) [95% CI] unless otherwise indicated.

Intracytoplasmic Sperm Injection and Reproductive Outcomes

To the Editor Dr Boulet and colleagues1 reported rapid increases in national use of intracytoplasmic sperm injection (ICSI) over the last 2 decades, especially among non–malefactor infertility.

Their analysis relied on diagnoses of male factor infertility reported by IVF centers and not specific semen analysis parameters, which the US Centers for Disease Control and Prevention (CDC) does not track. However, the definition of abnormal semen parameters and therefore the primary indication for ICSI changed during the study period. The World Health Organization criteria were revised in 1999 and again in 2010,2 resulting in increasingly strict criteria and fewer abnormal semen analyses.

The consequence should have been less male factor infertility diagnoses and lower use of ICSI. Yet male factor infertility in CDC reports paradoxically increased during the study period from 16% in 1997 to 34% in 2012,3 raising doubts about the validity of this diagnosis. The pool of patients pursuing IVF likely changed as ICSI became more widely available. In addition, subfertile men with low morphology may not be reported to the CDC as infertile, even though low morphology is closely associated with poor fertilization4 and represents an indication for ICSI.

Intracytoplasmic sperm injection is principally a procedure to optimize fertilization rates. In addition, ICSI offers diagnostic benefits by stripping oocytes of surrounding granulosa cells in preparation for ICSI, and information about egg quality is gained, which can affect treatment decisions downstream. Despite an aging and increasingly complex infertility population, IVF success rates in the United States have improved during the past 2 decades and ICSI likely played a role in this improvement.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. All authors disclosed no conflicts.


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In Reply As noted in our article, the lack of information on the details of the male factor evaluation, including results of semen analyses, is a limitation of the study. Even though it is possible that some male factor infertility diagnoses were misclassified due to inaccurate reporting or temporal changes in the criteria for defining an abnormal semen analysis, we note that the discrepancy rate (the proportion of assisted reproductive technology cycles with incorrectly reported diagnosis) for male factor infertility in the CDC’s National Assisted Reproductive Technology Surveillance System (NASS) has remained consistently low (around 4%) with most of the difference due to underreporting.1

In addition, it is unlikely that misclassification of subfertile men with low morphology but no reported male factor infertility would have substantially affected our findings because low morphology has been found to have little effect on clinical outcomes in cycles in which ICSI was used.2 Furthermore, we found increasing trends in ICSI use for a number of non–male factor indications, thereby suggesting that misclas-