PHARMACOTHERAPEUTIC MANAGEMENT OF SICKLE CELL DISEASE

BACKGROUND

Sickle cell disease (SCD) is a term used to describe a group of genetic red blood cell disorders affecting hemoglobin. Hemoglobin is a protein in red blood cells that carries oxygen through the body. Red blood cells are normally disc shaped allowing them to be flexible and move freely through blood vessels delivering oxygen. In individuals with SCD, abnormal hemoglobin strands cause red blood cells to become an irregular, sickle shape. These sickle-shaped red blood cells are not flexible and can cause blockages slowing the flow of blood.

Sickle cell disease affects approximately 100,000 Americans.[1] It is primarily found in individuals of African, Mediterranean and Asian descents.[2] Although SCD is associated with high morbidity, currently 90 percent of children diagnosed with SCD survive into adulthood.[3] Pain and acute chest syndrome (ACS) are common complications associated with SCD. Pain, the most common symptom of SCD, can be characterized as acute or chronic.

As there is no cure for SCD, proactive management of SCD complications is a mainstay of therapy. For over 20 years, hydroxyurea has been the primary pharmacotherapeutic agent available for preventing SCD complications. Hydroxyurea increases fetal hemoglobin, reduces "sickling" of red blood cells, and improves blood flow.[4] In 2014 the Expert Panel Report on Evidenced-Based Management of Sickle Cell Disease recommended a treatment protocol for the utilization of hydroxyurea.[5] With each recommendation, the panel listed strength of recommendation and quality of evidence based on:

- protocols used in published clinical trials and observational studies,
- indirect evidence derived from basic science and pharmacokinetics of hydroxyurea, and
- a consensus process

The Expert Panel's recommended treatment protocol is summarized in Figure 1.

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[1] Minniti CP, Lu K, Groninger H. Pain in sickle cell disease. *J Palliat Med* 2013; 16:697-9.

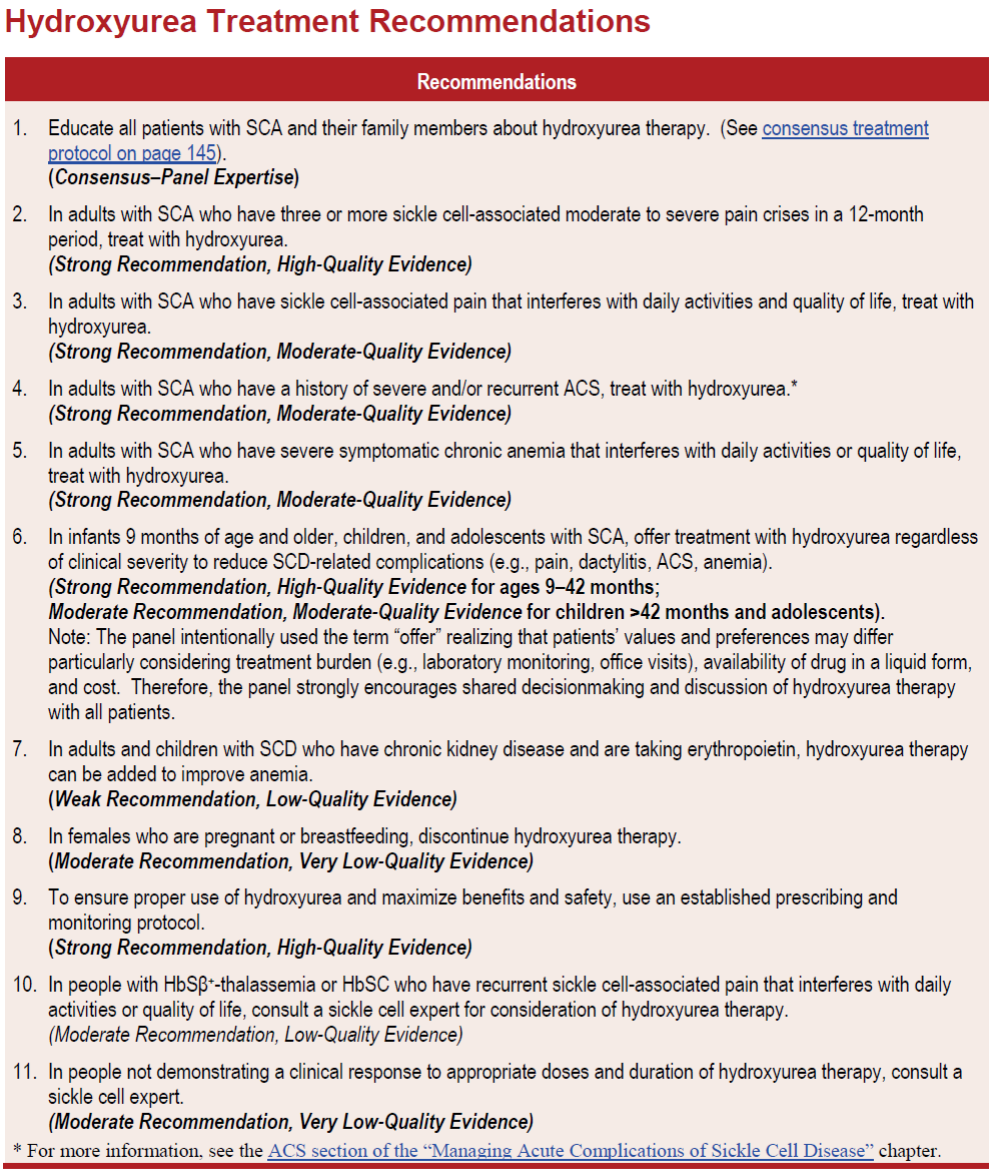
[2] Kanter J, Kruse-James R. Management of sickle cell disease from childhood through adulthood. *Blood Rev* 2013: 27: 279-87.

[3] US Department of Health and Human Services, National Institutes of Health. Evidence-based management of sickle cell disease. Expert panel report, 2014: 1. http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines/. (Accessed April 2018).

[4] Green NS, Barral S. Emerging science of hydroxyurea therapy for pediatric sickle cell disease. *Pediatr Res* 2014; 75: 196-204.

[5] US Department of Health and Human Services, National Institutes of Health. Evidence-based management of sickle cell disease. Expert panel report, 2014:77 . http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines/. (Accessed April 2018).

Figure 1: Evidence-Based Hydroxyurea Treatment Recommendations



Hydroxyurea Treatment Recommendations

Recommendations

1. Educate all patients with SCA and their family members about hydroxyurea therapy. (See consensus treatment protocol on page 145).
   (***Consensus–Panel Expertise***)
2. In adults with SCA who have three or more sickle cell-associated moderate to severe pain crises in a 12-month period, treat with hydroxyurea.
   (Strong Recommendation, High-Quality Evidence)
3. In adults with SCA who have sickle cell-associated pain that interferes with daily activities and quality of life, treat with hydroxyurea.
   (Strong Recommendation, Moderate-Quality Evidence)
4. In adults with SCA who have a history of severe and/or recurrent ACS, treat with hydroxyurea.*
   (Strong Recommendation, Moderate-Quality Evidence)
5. In adults with SCA who have severe symptomatic chronic anemia that interferes with daily activities or quality of life, treat with hydroxyurea.
   (Strong Recommendation, Moderate-Quality Evidence)
6. In infants 9 months of age and older, children, and adolescents with SCA, offer treatment with hydroxyurea regardless of clinical severity to reduce SCD-related complications (e.g., pain, dactylitis, ACS, anemia).
   ***(Strong Recommendation, High-Quality Evidence* for ages 9–42 months;**
   ***Moderate Recommendation, Moderate-Quality Evidence* for children >42 months and adolescents).**
   Note: The panel intentionally used the term "offer" realizing that patients' values and preferences may differ particularly considering treatment burden (e.g., laboratory monitoring, office visits), availability of drug in a liquid form, and cost. Therefore, the panel strongly encourages shared decisionmaking and discussion of hydroxyurea therapy with all patients.
7. In adults and children with SCD who have chronic kidney disease and are taking erythropoietin, hydroxyurea therapy can be added to improve anemia.
   (Weak Recommendation, Low-Quality Evidence)
8. In females who are pregnant or breastfeeding, discontinue hydroxyurea therapy.
   (Moderate Recommendation, Very Low-Quality Evidence)
9. To ensure proper use of hydroxyurea and maximize benefits and safety, use an established prescribing and monitoring protocol.
   (Strong Recommendation, High-Quality Evidence)
10. In people with HbSβ⁺-thalassemia or HbSC who have recurrent sickle cell-associated pain that interferes with daily activities or quality of life, consult a sickle cell expert for consideration of hydroxyurea therapy.
    (Moderate Recommendation, Low-Quality Evidence)
11. In people not demonstrating a clinical response to appropriate doses and duration of hydroxyurea therapy, consult a sickle cell expert.
    (Moderate Recommendation, Very Low-Quality Evidence)

* For more information, see the ACS section of the "Managing Acute Complications of Sickle Cell Disease" chapter.

In July 2017, the U.S. Food and Drug Administration (FDA) approved L-glutamine (Endari®), the first new therapeutic agent for treating SCD in over two decades.[6] Endari is approved for use in patients ≥ 5 years to reduce acute complications of sickle cell disease. Preliminary data suggests Endari can reduce painful events, acute chest syndrome events, and hospitalizations. [7] In the clinical trials, most patients studied

[6] FDA. FDA approves new treatment of sickle cell disease. July 2017. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm566084.htm. (Accessed April 2018).

[7] FDA. Oncologic drugs advisory committee: advisory committee briefing materials. May 24, 2017. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM559736.pdf. (Accessed April 2018)

were also receiving hydroxyurea. Endari was approved through the orphan drug designation and is distributed through specialty pharmacies.

MS-DUR conducted an analysis of the treatment of Mississippi Medicaid beneficiaries with SCD. The primary objectives were to examine hydroxyurea utilization and any Endari claim approvals through March 2018. This analysis, along with clinical trial data and expert panel recommendations, will serve as references in the development of recommendations in the treatment of SCD in Mississippi Medicaid beneficiaries.

METHODS

MS-DUR identified all Mississippi Medicaid beneficiaries with a diagnosis of SCD (ICD-10 D57 – excluding D57.4 sickle cell trait) present on a medical claim paid anytime between July 2016 and March 2018. Pharmacy claims for hydroxyurea or Endari paid between January 2017 and March 2018 were extracted for these beneficiaries.

RESULTS

Table 1 shows the characteristics of beneficiaries identified with SCD through medical claims. Almost half (54%) of the SCD patients were adults (ages 21 and above) and over a fourth (28%) were children ages $\leq$ 6 years.

Hydroxyurea, Endari and narcotics can be used for treatment of pain associated with SCD. Only one (1) prescription claim for Endari had been paid at the time of this analysis. Over half of the beneficiaries with SCD had not received a prescription for hydroxyurea or narcotics during the last year. Of those that had received prescriptions that could have been for pain, most were being treated with narcotics only. Although the ages of beneficiaries with SCD varied amongst the fee-for-service (FFS) and the coordinated care plans (CCOs), the treatment patterns for SCD did not meaningfully vary across pharmacy programs.

TABLE 1: Characteristics of Medicaid Beneficiaries With Sickle Cell Disease*
(January 2017 - March 2018)

		Pharmacy Program							
		FFS		UHC		MAG		TOTAL	
TOTAL		1,312		1,725		1,936		4,973	
Age	0 - 6	128	10%	595	34%	649	34%	1,372	28%
	7-13	131	10%	260	15%	285	15%	676	14%
	14 - 18	109	8%	166	10%	188	10%	463	9%
	19 - 20	88	7%	74	4%	60	3%	222	4%
	21 +	855	65%	630	37%	754	39%	2,239	45%
Products Prescribed for Pain	No Rx	793	60%	991	57%	1,084	56%	2,868	58%
	Hydroxyurea only	25	2%	36	2%	32	2%	93	2%
	Hydroxyurea and narcotics	85	6%	160	9%	212	11%	457	9%
	Narcotics only	409	31%	538	31%	608	31%	1,555	31%

** At least one medical claim had a diagnosis code of D57 Sickle Cell Disases -- excluding D57.4 Sickle Cell Trait.*

Table 2 illustrates use of hydroxyurea by beneficiary age for those beneficiaries continuously enrolled in the last four months included in the analysis. There are just over 4,000 beneficiaries currently enrolled that have SCD. The currently enrolled beneficiaries represent 82% of all beneficiaries with SCD that have been enrolled in Medicaid for any length of time during the last year. This indicates that the SCD population in Medicaid is fairly stable and many of these patients will remain enrolled; thus managing progression of the disease is critical.

Although younger children were somewhat less likely to be treated with hydroxyurea, use of the product was very low for all ages. Overall, 88% of beneficiaries with SCD were not treated with hydroxyurea between January 2017 and March 2018.

TABLE 2: Number of Claims for Hydorxyurea Paid Between January 2017 and March 2018 by Age
(ONLY includes beneficiaries continously enrolled December 2017 - March 2018; FFS and CCOs)

Age (years)	Number of Claims for Hydroxyurea *(Percentages are of each age group)*										Total
	0		1 - 2		3 - 5		6 - 10		11 +		
0 - 6	1,101	93%	27	2%	31	3%	14	1%	7	1%	1,180
7 - 13	471	78%	31	5%	33	5%	39	6%	32	5%	606
14 - 18	322	81%	21	5%	24	6%	22	6%	11	3%	400
19 - 20	122	84%	6	4%	7	5%	6	4%	5	3%	146
21 +	1,539	89%	70	4%	56	3%	47	3%	14	1%	1,726
Total	3,555	88%	155	4%	151	4%	128	3%	69	2%	4,058

Table 3 shows the number claims for hydroxyurea and narcotics for beneficiaries with SCD who were continuously enrolled during the last four months of the analysis. Overall, 37% of SCD patients were treated with narcotics while receiving no prescriptions for hydroxyurea. It should be noted that 13% of all beneficiaries receiving narcotics received 6 or more prescriptions for narcotics in this timeframe. Thus these beneficiaries can be classified as being chronically treated with narcotics.

TABLE 3: Number of Claims for Hydorxyurea and Narcotics Paid Between January 2017 and March 2018
(ONLY includes beneficiaries continously enrolled December 2017 - March 2018; FFS and CCOs)

Percentages are of total		Number of Claims for Narcotics										TOTAL	
		0		1 - 2		3 - 5		6 - 10		11 +			
Number of Claims for Hydroxyurea	0	2,242	55%	832	21%	216	5%	108	3%	157	4%	3,555	88%
	1 - 2	19	0%	40	1%	30	1%	25	1%	41	1%	155	4%
	3 - 5	21	1%	36	1%	17	0%	23	1%	54	1%	151	4%
	6 - 10	20	0%	26	1%	27	1%	17	0%	38	1%	128	3%
	11 +	14	0%	16	0%	13	0%	11	0%	15	0%	69	2%
	TOTAL	2,316	57%	950	23%	303	7%	184	5%	305	8%	4,058	100%

CONCLUSIONS AND RECOMMENDATIONS

Endari should provide a new treatment alternative for pain associated with SCD. However, Endari is recommended as (a) adjunctive therapy with hydroxyurea when treatment with hydroxyurea alone is not adequate or (b) as monotherapy when a patient cannot tolerate hydroxyurea. Two major conclusions from this analysis are:

- Hydroxyurea appears to have limited utilization in the SCD population.
- Narcotics are being over-utilized to treat pain associated with SCD and appear to be used instead of hydroxyurea rather than in conjunction with hydroxyurea.

***Recommendations*:**

1. MS-DUR should implement an educational initiative encouraging the utilization of hydroxyurea, as referenced in **Figure 1**, for the proactive management of sickle cell complications such as pain and ACS while discouraging the inappropriate use of narcotics. The educational initiative should also address the role of Endari in the management of SCD.

2. Endari should be prescribed for use in addition to hydroxyurea unless intolerance or contraindication of hydroxyurea has been documented.

3. DOM Office of Pharmacy should implement manual PA criteria for Endari use.