Sickle Cell Disease

an Overview

11th Annual Sickle Cell Disease and Thalassemia Conference

11 October 2017

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Outline of Overview

- Sickle cell disease (SCD) pathophysiology
- Complications of SCD *(to be discussed in this conference)*
- Interventions for SCD *(to be discussed in this conference)*
- “Old” agent: hydroxyurea *(but unanswered questions)*
- New approach: Implementation Science
- “New” agent: L-glutamine *(2nd drug approved by FDA)*
Pathophysiology of Sickle Cell Disease

**Stem Cell Transplant**

**Gene Therapy**

**HU → ↑ HbF**

**Reduced by chronic transfusion**

**Hemolysis**

**Vasoocclusion**

**Arginine** → **Ornithine** → **Citruline**

**Arginase**

**NO Synthase**

**NO** → **NO₃**

**HbS solution** → **HbS polymer**

**Oxygenated** → **Deoxygenated**

**Valine residue**

**GAG** → **β6 Glu** → **β6**

**β6 Triplet codon**

**T** → **G**
Complications of Sickle Cell Disease

- Stroke, silent infarcts, neurocognitive and sleep problems (Gordon, Kirkham, Kanter)
- Retinopathy
- Pulmonary Hypertension (Klings)
- Cardiac (Quinn)
- Acute chest syndrome (McMahon, Greenough)
- Spleen problems
- Kidney Dysfunction (Sharpe, Campbell)
- Enuresis (Pelidis)
- Avascular necrosis of hip
- Gallstones
- Priapism
- Leg ulcers (Minniti)

Hematology

Growth and maturation (Campbell)

Pain (Anand, Darbari)

Infections

Psychosocial issues (Treadwell, Porter, Rowle, Hsu)

Multiorgan failure (Howard)
Current Questions Related to Hydroxyurea

- Does hydroxyurea affect brain function?
- What influences decision-making about hydroxyurea?
- What is the optimal dosing of hydroxyurea?
- What is the role of hydroxyurea in low and middle income countries? *to be addressed later*
Effects of Hydroxyurea on Neurocognitive Performance in Children with SCD  
(Wang, Schreiber, et al., 2017)

- Only one study has reported improvement in global cognitive index from HU. (*Puffer, Child Neuropsych*, 2007)
- As part of protocol SCDMR4, we prospectively evaluated school age children who were being started on HU treatment.
- Treated subjects (n=21) had HbSS or Sβ0thal and were 7-18 y.o.; controls (n=11) declined HU treatment.
- In treated subjects, but not in controls, mean FSIQ was significantly higher after one year of HU (80.9→83.4)
- In treated subjects, but not in controls, comprehension of word passages on the Woodcock-Johnson Achievement test were improved (78.7→82.6)
WISC IV Scores for Patients Treated with HU

* P <0.05
Woodcock-Johnson III Achievement Scores for Patients Treated with HU

* P <0.05
Effects of HU on Neurocognition - Summary

- Overall, results indicated that HU treatment for one year was associated with improved cognitive functioning (~ 2.5 points on FSIQ) and improved passage (reading) comprehension.

- The control group did not show improvement in cognitive skills. (Although not statistically significant, most scores declined with small to medium effect sizes.)

- Longitudinal study is needed to examine the durability of this HU effect.

- Future cognitive and academic intervention trials are needed to examine the impact of other treatment methods besides HU (or in addition to HU).
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.
Ten years ago, preferences of parents of children with severe SCA were: HU 70%, chronic transfusion 17%, BMT 10%, undecided 3% (Hankins, PBC, 2007).

More recently, structured interviews conducted and qualitatively analyzed for caregivers who had chosen (n=9) or declined (n=10) HU for their child with SCD.

Common themes among caregivers: difficulty coping with having a child with SCD, fearfulness about starting HU therapy, need for more information about SCD.

Caregivers who chose HU: sought more detailed information about SCD and HU, perceived HU treatment as a way to prevent complications and extend their child’s life.

Caregivers who declined HU: admitted poor understanding of SCD, would only consider HU if child had more severe future complications, did not ask questions of their providers.
**HU and Shared Decision Making: Recommendations**

- *Creary:* Providers should give all families the same information on HU, such as the reasons for wanting to start treatment, the length of time to expect before HU may begin to reduce symptoms, and the importance of regular HU adherence; develop decision aid tools; support the consensus that HU is a standard-of-care treatment.

- *Crosby, et al. (PBC, 2015):* NHLBI guidelines → how to navigate the discussion of preventive disease-modifying treatment for asymptomatic children with SCA?
  
  - Ask the family to invite all persons involved in the decision to initiate HU to attend a clinic appointment, or talk with the medical team via Skype or phone.
  - Provide education about HU use in SCA and/or refer to trustworthy internet resources.
  - Address safety concerns.
  - Mention HU as a preventive treatment during the child’s initial visits with the goal of offering it as a treatment option once the child is ≥ 9 months old.
  - Plan multiple follow-up conversations about HU.
  - Develop and provide a HU treatment protocol that includes labs to monitor toxicity and adherence, lab draw intervals, and methods for promoting adherence.
Physician Perspective of Treatment-Related Decision Making

Bakshi, et al., PLOS One, 2017

- Informing patients to assist in decision making
- Discussing all possible treatment options
- Emphasizing treatment as one of the options

- Informing patients to convince for predetermined treatment
- Determine timing and type of treatment discussed
- Strong advocate for particular treatment when disease is severe

Disease Severity
Intensity of Treatment
Urgency of Treatment
Benefits of hydroxyurea are primarily due to increased HbF.

Laboratory benefits thought to be dose-dependent?
- Escalation >25 mg/kg/d → HbF ~20%
- Non-escalated ~20 mg/kg/d → HbF ~15%

Drug exposure (pharmacokinetics) is similar in younger and older children; liquid and capsular formulations are bioequivalent.

Ware & Aygun, ASH Educational Book 2009;1:62-69
Estepp and Neville; 2015
Hydroxyurea management in kids: intensive versus stable dosage strategies (HUG KISS) (J. Estepp, PI)

- Single-blind, multicenter trial
- $1^0$ endpoint: HbF level
- Goal for enrollment/follow-up:
  - 50 participants (9-36 m.o.) in feasibility trial (R34)
  - 12 months of follow-up
- Randomization arms:
  - Intensive dosing:
    - Start at 20 mg/kg/d
    - ↑ by ~5 mg/kg/day q 8 wk
    - Goal ANC of 1500-3000/μL
    - Max dose of 35 mg/kg/day
  - Stable dosing:
    - Maintain at 20 mg/kg/day
HUG-KISS – Current Status

- Protocol opened at 4 sites (St. Jude, Children’s Hospital of Atlanta, University of Mississippi, University of Texas at Southwestern)
- Liquid formulation tested and stable at room temperature
- Total of 14 patients enrolled; 7 patients randomized to stable vs. MTD dosing
- Phase 3 trial to be conducted if current trial demonstrates feasibility after 2 years
Low Dose Hydroxyurea in Indian Children with Sickle Cell Anemia
(Jain, Indian Ped, 2013)

- Study cohort: 144 children (<18 y.o.) with severe SCA
- Fixed low dose of HU (10 mg/kg/d) x 2 years
- Results: ↑ HbF, Hb, MCV; ↓ VOC, ACS, transfusions, sequestration, hospitalizations
- Conclusions: Fixed low dose HU effective and safe in some Indian children with SCA
Hydroxyurea Trials in Low and Middle Income Countries
SCD and Implementation Science
(King and Baumann, PBC 2017; 64:e26649)

- Center for Translation Research and Implementation Science (CITRIS) formed in 2014 at NIH/NHLBI.
- Implementation Research = “The scientific study of the use of strategies to adopt and integrate evidence-based health interventions into clinical and community settings in order to improve patient outcomes and benefit population health.”
- SCD lacks an infrastructure for intervention trials → significant delay in implementing new methods of care.
- Examples of timelines of randomized controlled trials and time to reach standard of care:
1998
STOP Phase III Trial published supporting TCD screening

2015
40% of children are getting TCD

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https://doi.org/10.1002/pbc.26449
Examples of Investigation in Sickle Cell Disease – How long did it take?

21 years of investigation: original concept to publication of Silent Infarct Transfusion trial

1993
Significance of cognitive impairment with silent infarcts

1999
Doris Duke funds grant for silent stroke screening

2008
Feasibility trial Single arm blood for silent infarcts published

2009
SIT Trial funded by NINDS

2014
SIT Trial published supporting screening and transfusion

Stroke With Transfusion Changing to Hydroxyurea

1999
Publication of prospective use of hydroxyurea as alternative to discontinuing blood transfusion for stroke

2004
Feasibility trial Single arm blood for silent infarcts published

2005
SWITCH Trial funded by NHLBI

2012
SWITCH trial published concluding that hydroxyurea was not superior to transfusion and chelation
Trial closed at interim analysis

Implementation Science: Recommendations

- Examine the quality gap (between guidelines and practice)
- Identify implementation strategy ("a systematic intervention to adopt and integrate evidence-based health innovations into usual care")
- Select an implementation theory, conceptual model, and/or framework
- Measure implementation outcomes
Sickle Cell Disease Implementation and Dissemination Consortium (SCDIC) NHLBI 1U01HL133993
SCDIC Goals: National vs. Local Goals

Goals of the National Consortium:
To use Implementation Science to identify and address barriers to quality care in SCD

Goal of the Memphis Project:
To improve Hydroxyurea adherence in SCD patients by integrating text messages into medical homes
SCDIC - Project Phases

- **Phase I:** Needs assessment of the barriers of care for patients with SCD and develop registry of SCD patients with clinical and patient-reported outcomes

- **Phase II:** Implementation science-driven studies to address gaps found in needs assessment
Glutamine - Background

- Non-essential amino acid
- Precursor in synthesis of other amino acids (including arginine), glucose, and nicotinamide adenine dinucleotide (NAD)
- Used in clinical management of burns, trauma, and low birth weight infants as nutritional supplement
- In SCD, shown to increase NAD redox potential, decrease endothelial adhesion, and decrease resting energy expenditure (with improved weight gain)
Glutamine Study Design
(from FDA submission by Emmaus Medical Inc)

- SS
- Sickle β^0^-thalassemia
- ≥5 years old
- ≥2 SCC prior 12 mos
- HU use permitted
- Transfusions allowed

<table>
<thead>
<tr>
<th>L-glutamine 0.3 g/kg BID</th>
<th>2:1 ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=152</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Placebo 0.3 g/kg BID</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N=78</td>
<td></td>
</tr>
</tbody>
</table>

48 week treatment period

Randomization
Stratified by Hydroxyurea use and Region

3 wk Taper
End Treatment Follow-up visit
Glutamine Trial: Time to First Crisis

Survival Probability

First Sickle Cell Crisis (Days)

L-gln  151  91  59  40  31  22  19  3  0
Pbo   78  41  23  16  9  8  5  0

HR = 0.69
95% CI (0.52 – 0.93)
p = 0.0152

Median days: 84 vs 54
### Glutamine Trial: Summary of Efficacy Results

<table>
<thead>
<tr>
<th>Descriptive results</th>
<th>SCCs (median)</th>
<th>Time to onset of first crisis (days)</th>
<th>Acute Chest Syndrome (mean)</th>
<th>Hospitalizations (median)</th>
<th>Cumulative Days Hospitalized (median)</th>
<th>Blood transfusion events (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-glutamine</td>
<td>3</td>
<td>84</td>
<td>0.1</td>
<td>2</td>
<td>6.5</td>
<td>1.42</td>
</tr>
<tr>
<td>Placebo</td>
<td>4</td>
<td>54</td>
<td>0.3</td>
<td>3</td>
<td>11.0</td>
<td>2.32</td>
</tr>
<tr>
<td>Difference</td>
<td>-1</td>
<td>30 days</td>
<td>-0.2</td>
<td>-1</td>
<td>-4.5</td>
<td>-0.9</td>
</tr>
<tr>
<td>% difference</td>
<td>25%</td>
<td>56%</td>
<td>67%</td>
<td>33%</td>
<td>41%</td>
<td>39%</td>
</tr>
<tr>
<td>P-value(^a)</td>
<td>0.0052(^b)</td>
<td>0.0152(^c)</td>
<td>0.0028(^b)</td>
<td>0.0045(^b)</td>
<td>0.022(^d)</td>
<td>NA</td>
</tr>
</tbody>
</table>

SCC = sickle cell crisis, NA = not applicable.

\(^a\) P-value for between group difference.

\(^b\) CMH using modified ridit scores.

\(^c\) ANOVA model with treatment as the main effect.

\(^d\) Wilcoxon rank-sum test.
Glutamine Trial: Subgroup Analysis Rate Ratios by Age, Sex, and Hydroxyurea Use

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Favors L-gln</th>
<th>Favors Pbo</th>
<th>L-gln n</th>
<th>Pbo n</th>
<th>NBR Rate Ratio</th>
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</thead>
<tbody>
<tr>
<td>Age 5-12</td>
<td></td>
<td></td>
<td>34</td>
<td>17</td>
<td>0.52 (0.32, 0.85)</td>
</tr>
<tr>
<td>Age 13-18</td>
<td></td>
<td></td>
<td>41</td>
<td>26</td>
<td>1.46 (0.95, 2.25)</td>
</tr>
<tr>
<td>Age &gt;18</td>
<td></td>
<td></td>
<td>77</td>
<td>35</td>
<td>0.64 (0.46, 0.89)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td>73</td>
<td>33</td>
<td>0.73 (0.51, 1.05)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td>79</td>
<td>49</td>
<td>0.81 (0.59, 1.12)</td>
</tr>
<tr>
<td>HU Yes</td>
<td></td>
<td></td>
<td>101</td>
<td>52</td>
<td>0.77 (0.58, 1.03)</td>
</tr>
<tr>
<td>HU No</td>
<td></td>
<td></td>
<td>51</td>
<td>26</td>
<td>0.78 (0.51, 1.20)</td>
</tr>
</tbody>
</table>
Glutamine Trial: Conclusions

- In a phase III study, glutamine resulted in a significantly lower number of SCC compared to placebo.
- Glutamine cohort had lower frequencies of ACS and hospitalization.
- 2/3 of the patient population were receiving hydroxyurea.
- Safety profile of glutamine treatment similar to placebo.
- Benefit/risk assessment considered to be positive for both pediatric and adult patients.
PECULIAR ELONGATED AND SICKLE-SHAPED RED BLOOD CORPUSCLES IN A CASE OF SEVERE ANEMIA

JAMES E. HERBEE, M.D.
CHICAGO

This case is reported because of the unusual blood findings, no duplicate of which I have ever seen described. Whether the blood picture represents merely a freakish polychromatosis or is dependent on some peculiar physical or chemical condition of the blood, or is characteristic of some particular disease, I cannot at present answer. I report some details that may seem non-essential, thinking that if a similar blood condition is found in some other case a comparison of clinical conditions may help in solving the problem.

History.—The patient was an intelligent negro boy of 12, who had been in the United States three months, during which time he was a student in one of the professional schools in Chicago. His former residence had been Grenada, West Indies, where he had been born and brought up, one of a family of four children, all living, and all well with the exception of himself. His mother was living and in good health; his father had died of accident. At the age of 10 the patient had had yaws. This was a common disease in the locality where he lived. The lesion, as he described them, had been purulent, with formation of ulcers and ulcers. On healing, some of the ulcers had been as large as a silver quarter of a dollar. The disease lasted about one year and during this time he had felt somewhat weak and languid. Most of the ulcers had been on the legs and the patient himself had thought that this lesion of the lesion might have been due to the lesions and ulcers that were frequently produced as he ran about, a barefoot boy, through the streets and the streets. He was sure he had never had any blood-loss, though he said it was not uncommon in Grenada. He had attended school up to the age of 12. Since leaving school, that is, for the past three years, he had felt a dullness in the eyes. For about a year he had noticed some palpitation and shortness of breath which he had attributed to excessive smoking. There had been times when he thought he was bluish and when the whites of the eyes had been tinged with yellow. At such times he had not had any pain, chill or fever. Three years previously he had had a purulent discharge from the right ear lasting six months. He had had no diarrhea and no hemorrhages at any time. He looked weak and gaunt. There was never any dyspnea or other joint trouble. On leaving New York in September, 1904, he had a sore on one toe for which he consulted a physician. Treatment of inosil was applied and in a week the sore had healed, leaving a scar which the other on the limb. For the past five weeks he had been coughing. Two days prior to examination he had “taken cold,” his cough had been worse and he had had a slight chill, followed by fever. It was this cough and fever for which he wished treatment at the hospital, and of which he chiefly complained, though he mentioned also that he felt weak and dizzy, had headaches and return of the nose.

Fig. 2.—A laboratory at Presbyterian Hospital, Chicago, circa 1905.

The Presbyterian Hospital, Chicago, Ill.

EXAMINATION OF BLOOD.

<table>
<thead>
<tr>
<th>Case Number</th>
<th>12/31</th>
<th>12/31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of Patient</td>
<td>Noel</td>
<td></td>
</tr>
<tr>
<td>Shape</td>
<td>erythrocytes -</td>
<td>erythrocytes -</td>
</tr>
<tr>
<td>Red blood cells</td>
<td>2,500</td>
<td>2,800,000</td>
</tr>
<tr>
<td>Leucocytes per cmm. (Thomas' Ziem)</td>
<td>15,250</td>
<td>50%</td>
</tr>
<tr>
<td>Hemoglobin (Van Eman)</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>1020</td>
<td>1020</td>
</tr>
<tr>
<td>Color index</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Macrophotical and quantitative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythrocytes-Color</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucocytes-Apparant increase in number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratio of granular to non-granular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasmidum mallei</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
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<td></td>
</tr>
</tbody>
</table>

Fig. 3.—Ernest Irons' blood examination report on Walter Clement Noel, Dec 31, 1904, describing and depicting the oddly shaped red blood cells.
