Breaking the Sickle of Pain Crisis

Logan Olson, PharmD
PGY1 Pharmacy Resident
Pharmacy Grand Rounds
May 30th, 2017
Objectives

• Describe the pathophysiology of sickle cell disease and related pain crisis

• Outline current agents for treatment and prevention of sickle cell-related pain crises

• Discuss ongoing research regarding potential management options for pain crisis
Epidemiology

• Most common monogenic disorder
  • ~300,000 infants/year born with sickle cell anemia (homozygous for HbSS)

• Highest prevalence:
  - Sub-Saharan Africa
  - Mediterranean
  - Middle East
  - India

• US prevalence: ~100,000 persons

• Affects all ages
  • Symptoms typically begin at ~6 months of life

Objective 1

Describe the pathophysiology of sickle cell disease and related pain crisis
Pathophysiology

Hemoglobin A

α chain

β chain
Pathophysiology

- Single gene mutation

HBB gene

Nucleotide

CCT – GAG – GAG

Amino Acid

Proline

Glutamine

Glutamine

Normal HBB gene

Pathophysiology

• Single gene mutation

HBB gene

Nucleotide

CCT – GTG – GAG

Amino Acid

Abnormal HBB gene

Proline

Valine

Glutamine

Abnormal HBB gene

Pathophysiology

Hemoglobin S

α chain

Mutated β chain

Pathophysiology
Pathophysiology
Pathophysiology

- Poor oxygenation
- Acidosis
- Dehydration

Pathophysiology

Inflammation

Cell rigidity

Hemolysis

↓ NO

Acute Pain

Osteonecrosis

Stroke

Acute Chest Syndrome

Hyposplenism

Nephropathy


NO = Nitric Oxide
Case

• Ob Streperous, 24 year-old female
Case

• PMH:
  - Sickle cell disease
    - HbSS
  - Functional asplenia
  - 3 hospitalizations within the last 12 months for pain episodes

• Medications
  - Hydroxyurea 2,500mg daily (~35mg/kg)
  - Ibuprofen 800mg every 8h as needed
  - Oxycodone 5-10mg every 4 hours as needed
  - Penicillin V 250mg BID
Case question

• Which of the following is likely the cause of Ob Streperous’s pain?

  • A – Muscle pain secondary to aggressive gardening
  • B – Vaso-occlusions secondary to dehydration
  • C – Muscle cramping secondary to dehydration
  • D – Vaso-occlusions secondary to poor oxygenation
Objective 2

Outline current agents for treatment and prevention of sickle cell-related pain crises
Management

Treatment
- NSAIDS
- Opioids

Prevention
- Hydroxyurea

NSAIDS = Nonsteroidal Antiinflammatory Drugs

NHLBI. Expert Panel Report, 2014
Udezue and colleagues, 2007

Prospective observational study of 1,154 patients

Pain
- Morphine 5-7.5mg IV q4h x24h
- Concomitant use of oral analgesics

Oxygenation
- Oxygen by nasal cannula when saturation <95%

Hydration
- 2-3L oral fluid when possible
- D5W/0.45% NaCl 75-125 ml/hr x24h

Results: Acute pain crisis could be terminated and patients discharged within 72h in over 80% of cases


IV = Intravenous
van Beers and colleagues, 2007

**Population**
- Vaso-occlusive crisis (n=25)

**Design**
- Prospective, randomized

**Intervention**
- Continuous morphine infusion
- Morphine PCA

**Results**
- Conclusion: A similar reduction in pain was achieved in both groups, but less morphine was used and less side effects observed in the PCA group
IMPROVE PCA

Population: Vaso-occlusive crisis (n=22)

Design: Multi-center, randomized

Intervention:
- ↑ Demand Dose; ↓ Infusion Rate
- ↓ Demand Dose; ↑ Infusion Rate

Results:
Reduction of pain intensity and time to target improvement were similar between the two groups

HDLI = higher demand dose with low constant infusion
LDHI = lower demand dose and higher constant infusion

Pain Control

Severe Pain

Consider basal infusion

IV Analgesia

PCA

Morphine or Hydromorphone

Scheduled Doses

Reassess pain every 15-30 minutes until pain is under control per patient report, consider 25% dose escalation if pain uncontrolled

PCA = Patient Controlled Analgesia
Adjunct treatment

• Oxygen saturation <95%
  • Administer oxygen

• Blood transfusion or exchange
  • Only if other indications exist

• Dehydration
  • Intravenous replacement
  • Oral as possible
Prevention

• Hydroxyurea
  • Mechanism of action
    • Increases fetal hemoglobin
Prevention

- Hydroxyurea
Charache and colleagues, 1995

**Population**
Patients with 3+ pain crises in 12 months (n=299)

**Design**
Multicenter, randomized, double-blind

**Intervention**
- Hydroxyurea 15mg/kg
- Placebo

**Results**
Conclusion: Hydroxyurea reduced the yearly rate of painful crisis, hospitalizations, incidence of chest syndrome, and transfusion requirements

Hydroxyurea

- 15 mg/kg/day
  - ↑ dose by 5mg/kg/day every 8 weeks
    - Maximum dose: 35 mg/kg/day
  - ≥3 pain crises in 12-month period

- Tolerating?
  - Yes
    - ANCs ≥ 2,000 and Platelets ≥ 80,000
  - No
    - Hold therapy
      - Once blood counts recover, initiate at 5mg/kg lower than previous dose

ANC = Absolute Neutrophil Count

Case

• It has been determined Ob Streperous is having a pain crisis. She has already received 2L of LR and scheduled IV morphine in the ED. Which of the following should be recommended when she arrives to your unit?

• A – Oral oxycodone 5-10mg every 4 hours as needed
• B – IV morphine 5-7.5mg every 4 hours as needed
• C – Morphine PCA with a basal infusion of 2.5mg/hr, 0.5mg every 10 minutes with 10mg lockout every 4 hrs
• D – Continuous morphine infusion at 5mg/hr
Case
Mrs. Streperous is now hospital day 2 and has transitioned to oral pain medication. You notice her WBC = 2,800/ANC = 1,700 and the team is planning to discharge tomorrow continuing all home medications. Which of the following is an appropriate medication reconciliation intervention?

A – Hydroxyurea should be held until her ANC recovers
B – Oral pain medications should not be prescribed upon discharge
C – Ibuprofen should be removed from her home medications as it was ineffective at controlling her pain
D – Hydroxyurea dose should be increased in order to prevent recurrence of her pain crisis
Objective 3

Discuss ongoing research regarding potential management options for pain crisis
Rivipansel

- Mechanism of action
  - Pan-selectin inhibitor

Rivipansel

- Mechanism of action
  - Pan-selectin inhibitor

Telen and colleagues, 2015

Population: Vaso-occlusive crisis requiring hospitalization (n=76)

Design: Multi-center, randomized, double blind, phase II

Intervention:
- Rivipansel
- Placebo

Outcome: Time to vaso-occlusive crisis resolution from start of study medication

Results

**Time to Resolution**: P = 0.187

**Time to Oral Analgesia**: P = 0.089

**Hospital Length of Stay**: P = 0.093
Results

Mean Hourly IV Opioid Use by Day

Placebo vs Rivipansel

P = 0.01

MEU = Morphine Equivalent Units

Conclusion

- Rivipansel resulted in:
  - Faster resolution of pain crisis
  - Reduced length of stay
  - Reduced IV opioid requirements

- Most outcomes failed to reach statistical significance
  - Phase III trial currently recruiting

- Possibly an adjunct option for pain crisis treatment

Crizanlizumab

- Mechanism of action
  - P-selectin inhibitor

**SUSTAIN**

**Population**
 Patients with 2-10 pain crises in 12 months (n=198)

**Design**
 Multi-center, double blind, randomized, phase II

**Intervention**
- High-dose Crizanlizumab
- Low-dose Crizanlizumab
- Placebo

## Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>High-Dose Crizanlizumab (N = 67)</th>
<th>Low-Dose Crizanlizumab (N = 66)</th>
<th>Placebo (N=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29</td>
<td>29</td>
<td>26</td>
</tr>
<tr>
<td>Male</td>
<td>48%</td>
<td>45%</td>
<td>42%</td>
</tr>
<tr>
<td>HbSS Genotype</td>
<td>70%</td>
<td>71%</td>
<td>72%</td>
</tr>
<tr>
<td>Concomitant Hydroxyurea</td>
<td>63%</td>
<td>62%</td>
<td>62%</td>
</tr>
<tr>
<td>2-4 pain crises with the last 12 months</td>
<td>63%</td>
<td>62%</td>
<td>63%</td>
</tr>
<tr>
<td>5-10 pain crises with the last 12 months</td>
<td>37%</td>
<td>38%</td>
<td>37%</td>
</tr>
</tbody>
</table>

**Results**

**Cranies/Year**

<table>
<thead>
<tr>
<th>Category</th>
<th>Intention-to-treat</th>
<th>Previously 2-4 Crises/Year</th>
<th>Previously 5-10 Crises/Year</th>
<th>Concomitant Hydroxyurea</th>
<th>No Concomitant Hydroxyurea</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRIT</strong></td>
<td>HD Crizanlizumab</td>
<td>LD Crizanlizumab</td>
<td>Placebo</td>
<td>HD = High-Dose</td>
<td>LD = Low-Dose</td>
</tr>
<tr>
<td><strong>P = 0.01</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusion

- Crizanlizumab resulted in lower incidence of pain crises
  - Regardless of:
    - Previous crises/year
    - Hydroxyurea use
  - Adverse effects were similar between treatment and placebo groups

- Currently planning phase III trial
  - Projected filing date: 2020

Final question

• It is now 2021 and Ob Streperous has arrived at your clinic for management of her sickle cell disease. She reports 5 pain crises in the past year and is wondering if there is anything else she can take besides hydroxyurea to reduce this incidence. Which of the following could benefit Mrs. Streperous?

• A – Rivipansel
• B – Crizanlizumab
• C – Prasugrel
• D – None of the above would be beneficial
Summary

• Pain crisis is caused by vaso-occlusions due to the sickling of red blood cells and adhesion of leukocytes to endothelium

• Current treatment and prevention strategies rely upon opioids and hydroxyurea

• Rivipansel and Crizanlizumab represent promising therapies which could assist in the treatment and prevention of sickle cell pain crisis respectively
Breaking the Sickle of Pain Crisis

Comments/Questions?

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Sickle Cell Genotypes

Exhibit 1a. Typical Laboratory Findings in Sickle Cell Disease

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Hb* (g/dL)†</th>
<th>HbS (%)</th>
<th>HbA (%)</th>
<th>HbA2 (%)</th>
<th>HbF (%)</th>
<th>HbC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS</td>
<td>6–9</td>
<td>&gt;90</td>
<td>0</td>
<td>&lt;3.5</td>
<td>&lt;10</td>
<td>0</td>
</tr>
<tr>
<td>S0β-thalassemia</td>
<td>7–9</td>
<td>&gt;80</td>
<td>0</td>
<td>&gt;3.5</td>
<td>&lt;20</td>
<td>0</td>
</tr>
<tr>
<td>Spβ-thalassemia</td>
<td>9–12</td>
<td>&gt;60</td>
<td>10–30</td>
<td>&gt;3.5</td>
<td>&lt;20</td>
<td>0</td>
</tr>
<tr>
<td>SC</td>
<td>9–14</td>
<td>50</td>
<td>0</td>
<td>&lt;3.5</td>
<td>≤1.0</td>
<td>45</td>
</tr>
</tbody>
</table>

* Definitions for abbreviations are as follows: Hb = hemoglobin; HbS = sickle hemoglobin; HbA = normal adult hemoglobin; HbA2 = minor variant of adult hemoglobin; HbF = fetal hemoglobin; HbC = hemoglobin variant that causes manifestations of SCD when paired with HbS

† The hemoglobin values in this exhibit apply in the absence of a blood transfusion in the last 4 months, are not absolute, and are applicable to adults and children only (not newborns).
# Alternative Therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Status/Results</th>
<th>Conclusions</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanguinate*</td>
<td>Recruiting</td>
<td>-</td>
<td>NCT02672540 NCT02411708</td>
</tr>
<tr>
<td>Apixaban†</td>
<td>Recruiting</td>
<td>-</td>
<td>NCT02179177</td>
</tr>
<tr>
<td>GBT440†</td>
<td>Recruiting</td>
<td>-</td>
<td>NCT03036813</td>
</tr>
<tr>
<td>Vepoloxamer (MST-188)*</td>
<td>Mean duration of VOC 82h vs 78h</td>
<td>No effect</td>
<td>NCT01737814</td>
</tr>
<tr>
<td>IV Magnesium*</td>
<td>LOS for VOC 56h vs 47h</td>
<td>No effect</td>
<td>Brousseau DC, et al. <em>Blood</em> 2015;126(14):1651-1657</td>
</tr>
<tr>
<td>Eptifibatide*</td>
<td>VOC duration 3 vs 3 days</td>
<td>No effect</td>
<td>NCT00834899</td>
</tr>
</tbody>
</table>
# Alternative Therapies

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Conditioning</th>
<th>Numbers</th>
<th>Outcomes</th>
<th>Availability</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matched sibling donor HSCT</td>
<td>Myeloablative</td>
<td>500 – 1000</td>
<td>OS &gt;95% DFS 85-95% at 5 years</td>
<td>Europe, USA, India, Middle East, Southeast Asia</td>
<td>Arnold SD et al. Haematopoietic stem cell transplantation for sickle cell disease - current practice and new approaches. <em>BJH</em> 2016;174:515-25.</td>
</tr>
<tr>
<td>Matched sibling donor HSCT</td>
<td>Reduced intensity</td>
<td>30</td>
<td>OS &gt;95% DFS 87% at 3 years</td>
<td>Clinical trials in USA</td>
<td>Hsieh MM et al. Nonmyeloablative HLA-matched sibling allogeneic hematopoietic stem cell transplantation for severe sickle cell phenotype. <em>JAMA</em> 2014;312:48-56.</td>
</tr>
<tr>
<td>Unrelated cord blood HSCT</td>
<td>Reduced intensity</td>
<td>20 - 30</td>
<td>OS 87-94% DFS 37-50%</td>
<td>Clinical trials in USA</td>
<td>Kamani NR et al. Unrelated donor cord blood transplantation for children with severe sickle cell disease: results of one cohort from the phase II study from the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). <em>Biol Blood Marrow Transplant</em> 2012;18:1265-72.</td>
</tr>
<tr>
<td>Haploidentical-related donor HSCT</td>
<td>Reduced intensity</td>
<td>35</td>
<td>OS 75-100% DFS 38 – 57%</td>
<td>Experimental procedure and trials in USA and UK</td>
<td>Arnold SD et al. Haematopoietic stem cell transplantation for sickle cell disease - current practice and new approaches. <em>BJH</em> 2016;174:515-25.</td>
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</tbody>
</table>