The Importance of Clinical Trials in Sickle Cell Disease

September 17, 2011
• **Walter Clement Noel** (1884-1916) was born in Grenada to a wealthy family. Despite chronic health problems, Noel attended Harrison College in Barbados, completing his undergraduate studies in 1904. That year he sailed to New York; developing a leg ulcer during the week-long journey. In New York he was treated with topical iodine, and the leg wound quickly healed. Noel then traveled to Chicago, to be a dental student at the Chicago College of Dental Surgery.

• In November 1904, Noel developed respiratory problems, lasting more than a month. He sought medical attention at the Presbyterian Hospital in Chicago and was evaluated by an intern, **Ernest Irons** (1877-1959). Irons performed a peripheral blood smear, which was a relatively recent addition to the clinical testing battery, and noted that Noel's blood smear contained “many pear-shaped and elongated forms—some small.” Irons discussed **Dr. James Herrick**, his supervising physician. With supportive care, Noel eventually recovered.

• Throughout the next 2½ years, Noel experienced several illnesses: bronchitis, hospitalized for 2 months at the Frances Willard Hospital for “a bilious and muscular attack”, knee pain.

• Irons kept dutiful case notes and gave all these to Herrick at the end of his training. Irons later achieved distinction as a rheumatologist, and he was the president of the American College of Physicians and the American Medical Association in the 1940s.
• Herrick presented Noel's case (without giving any credit to Irons) at a national meeting in 1910 and published a detailed report later that same year, but then he turned his attention to other matters; he is customarily given credit for being the first to describe myocardial infarction in 1912.
• A few months after the Noel case was published, a second, similar case was described in rural Virginia; the patient was a cook and housemaid named Ellen Anthony.
• Despite his illnesses, Noel graduated from dental school in 1907 and then returned to Grenada to set up a private practice in the capital city of St George's. In April 1916, he overexerted himself. He attended a horse race on the far side of Grenada, traveled a considerable distance home, and bathed, all on the same day. He then developed a “chill,” followed by a serious respiratory infection. Noel's condition steadily worsened, and he died in May 1916 in his home, at the age of 32 years.
• **YEARS LATER**
  • By the early 1920s, enough experience had accumulated that Vernon Mason was able to name the illness *sickle cell anemia*.
  • By the 1940s, the inheritance pattern and physical chemistry of hemoglobin S were well enough understood that renowned scientist Linus Pauling (1901-1994) could call sickle cell anemia “the first molecular disease.”

Sickle Cell Anemia, a Molecular Disease

Linus Pauling, Harvey A. Itano, S. J. Singer, and Ibert C. Wells
Gates and Crellin Laboratories of Chemistry,
California Institute of Technology, Pasadena, California
Clinical trials are a set of procedures in medical research and drug development that are conducted to allow safety and efficacy data to be collected for health interventions (e.g., drugs, diagnostics, devices, therapy protocols).

These trials can take place only after satisfactory information has been gathered on the quality of the non-clinic safety, and Institutional Review Board/Ethics Committee approval is granted in the country where the trial is taking place.
Disclosures

Glycomimetics, Inc, the conference sponsor, sponsors the GMI-1070-201 clinical trial. Dr. Alvarez is the center investigator.
Sickle Cell Disease 101

Ofelia Alvarez, MD
Director, Pediatric Sickle Cell Program
University of Miami
Miami, Florida
Objectives

- Discuss the pathophysiology of sickle cell disease (SCD): What is the disease process?
- Review the recent advances in the treatment and prevention of the complications of SCD.
More than 300,000 babies with hemoglobinopathies are born worldwide every year.

Approximately 5% of the world’s population are carriers of a trait gene for hemoglobinopathies.

8% African-Americans have S trait.

1/375 African-Americans have SCD
What happens in sickle cell?

Illustration from Medical World News article, "Sickle Cell Anemia" December 3, 1971

Mutation in the 6th position of the beta globin chain
HbS β6 (glu → val)

HbS polymerizes under deoxy conditions

Polymerization results in sickled, non-deformable red blood cells

- **PAINFUL CRISIS**
- **ORGAN DAMAGE**

in-vivo, non-deformable red blood cells result in vaso-occlusion
Advances in Treatment and Prevention of the Complications of SCD
Pain is an subjective unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone cancer</td>
<td>85</td>
</tr>
<tr>
<td>Oral cavity cancer</td>
<td>80</td>
</tr>
<tr>
<td>Genitourinary cancer</td>
<td>75</td>
</tr>
<tr>
<td>Lymphomas</td>
<td>20</td>
</tr>
<tr>
<td>Leukemias</td>
<td>5</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>&gt;95</td>
</tr>
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</table>
Adult Respondents in the Pain in Sickle Cell Epidemiology Study [PiSCES] (Smith, 2010)

- Pain occurred in 54.5% of the 31,017 days surveyed.
- 29% of respondents had pain > 95% of the days surveyed.
- Pain with mean intensity 6 in a 10-point scale resulted in ER visits or hospitalization.
- Pain in the arm, shoulder, upper back, sternum, clavicle, chest, or pelvis was perceived as pain crisis.

Pain Dairies in Children and Adolescents (Dampier, 2002)

- Daily pain at home is less common in children.
- Children and adolescents (6-21 years) reported SCD pain in 8.4% of the time with other pain occurring 2.7% of the time, and both (other and SCD) 5.7% of the time.
- Oral analgesic was taken in 80% pain days.
Mechanisms of Pain

**NOCICEPTIVE**
- There is an identifiable pain stimulus that is potentially or actually damaging (tissue injury).
- Most often associated with acute pain.

**NEUROPATHIC**
- Results when there is a malfunction or injury in the peripheral or central nervous system.
- May result from prior nociceptive pain episodes.
Mechanisms of Nociceptive Pain Perception

Modulation of pain through descending fibers and inhibition of transmission by endorphins

Brain detects pain in the thalamus, hypothalamus, and the limbic system

Swelling

itching

fever

Tissue ischemia and damage

Inflammatory mediators

Serotonin

Bradykinin

Histamine

Prostaglandins

IL-1, Cytokines

Mechanisms of Nociceptive Pain Perception

Pain receptors (nociceptors) in A-δ and C peripheral nerve fibers

N-methyl-Daspartate (NMDA) receptor of the dorsal horn of the spinal cord, crossing to the spinothalamic tract

Musculocutaneous nerve

Cauda equina

Femoral nerve

Saphenous nerve

Peroneal nerve

Digital nerves
Factors Promoting Pain

- **Environmental factors**
  - Higher wind speeds
  - Colder seasons
  - Higher barometric pressures
- **Genetic predisposition**
- **Psychological factors**
  - Negative impact of sense of “catastrophe”
  - Depression
Acute Chest Syndrome
Acute Chest Syndrome

- ACS occurs frequently during acute pain episodes
- Lung infarct or fat embolus or infection
- Phospholipase A2 hydrolizes phospholipids to produce free fatty acids and lysophospholipids, that cause lung injury.
- Minimized with incentive spirometry, controlling pain adequately without oversedation.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Number of episodes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia pneumoniae</td>
<td>71 (29%)</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>51 (20%)</td>
</tr>
<tr>
<td>RSV</td>
<td>26 (10%)</td>
</tr>
<tr>
<td>Staph aureus</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>11 (4%)</td>
</tr>
<tr>
<td>Mycoplasma hominis</td>
<td>10 (4%)</td>
</tr>
</tbody>
</table>

Vichinsky, National Acute Chest Syndrome Study, 2000
Stroke
Stroke with Transfusions Changing to Hydroxyurea (SWiTCH)

- Stroke occurs in 5-10% of children with SCA
- Standard treatment: Indefinite chronic transfusions.
- 133 children with SCA and history of stroke were randomized to continue on chronic transfusions plus deferasirox or switch to HU and phlebotomy (alternative arm)
- Blood transfusions and deferasirox arm was superior to HU and phlebotomy to prevent recurrent stroke (0 vs. 7 recurrent strokes) and resulted in equivalent iron liver content after 30 month-study time.
N=2000 ages 2-16 TCD screening

9% >200 cm/sec in MCA or ICA

Standard care
11 strokes

Blood transfusion
Hb S<30%
1 stroke
Hydroxyurea as Preventive Drug
Inhibition of HbS polymerization

Increased \( \gamma \)-globin synthesis

Decreased PS exposure
Decreased cation loss
Decreased expression of adhesion molecules

Decreased expression of adhesion molecules

Decreased neutrophil count

Vascular Endothelium

Myeloid Cells


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood markers</strong></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin level</td>
<td>Increase (high-grade evidence)</td>
</tr>
<tr>
<td>Percentage of fetal hemoglobin</td>
<td>Increase (high-grade evidence)</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>Increase (high-grade evidence)</td>
</tr>
<tr>
<td>Leukocyte count</td>
<td>Increase (high-grade evidence)</td>
</tr>
<tr>
<td><strong>Clinical outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>Pain crises</td>
<td>Decrease (high-grade evidence)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>Decrease (high-grade evidence)</td>
</tr>
<tr>
<td>Blood transfusion therapy</td>
<td>Decrease (high-grade evidence)</td>
</tr>
<tr>
<td>The acute chest syndrome</td>
<td>Decrease (high-grade evidence)</td>
</tr>
<tr>
<td>Priapism</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Stroke</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Leg ulcer</td>
<td>Not significantly different</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Not evaluated</td>
</tr>
<tr>
<td><strong>Prevention of end-organ damage</strong></td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Kidney</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Brain (cerebral blood flow)</td>
<td>Being evaluated</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>Decrease (low-grade evidence)</td>
</tr>
</tbody>
</table>
Hydroxyurea Reduces Mortality Among Children with SCA (Lobo, Brazil, 2010)

- HU offered to children with all genotypes ≥ 3 years if:
  - ≥ 2 ACS or ≥ 3 pain episodes in 1 year
  - Persistent O2 saturation <94%
  - Growth delay
  - Recurrent priapism
  - Sickle retinopathy
  - TCD velocity >200cm/sec or overt stroke with transfusion contra-indicated or family refusal

- Treatment group: 224 treated children and 741 untreated
  - Median duration of treatment 1.9 years (1.2-6 years)
  - Median HU dose 20 mg/kg/day (15-28)
## Comparison of HU-treated children (aged 3-18 years) vs. Untreated

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>Reduction in morbidity with HU treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>67.9% reduction</td>
<td>0.002</td>
</tr>
<tr>
<td>ER visits</td>
<td>48.7% reduction</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transfusions</td>
<td>36.3% reduction</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SURVIVAL</th>
<th>Survival to be 10 years old</th>
<th>Survival to be 18 years old</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyurea-treated</td>
<td>99.4% (95% CI, 98.2-100%)</td>
<td>97.4% (95% CI, 93.3-100%)</td>
<td></td>
</tr>
<tr>
<td>Untreated group</td>
<td>97.4% (95% CI, 96.6-98.6%)</td>
<td>66.3% (95% CI, 51.6-85.3%)</td>
<td>0.027</td>
</tr>
</tbody>
</table>
Barriers to the use of hydroxyurea (any daily treatment)

- Fear of bad side effects
- Frequent monitoring
- Cost
- Daily treatment (tired of being adherent, not to take the drug may give false sense of feeling “normal”)
Stem cell Transplantation

Bone marrow transplant

1. When a matched donor has been found some of their bone marrow is extracted from their hip, via a needle. Meanwhile, the recipient has had all their stem cells destroyed and receives blood transfusions until they are ready to receive new stem cells.
2. The extracted bone marrow is treated to remove the 'adult' cells.
3. The purified stem cells are then collected for transplant.
4. The stem cells are injected via a central line, and re-populate the bone marrow. Within a few months the 'new' bone marrow will start to produce 'healthy' blood cells.
The NMDP Registry (7 million total)

- Caucasian - 73% (5 million)
- Hispanic/Latino - 10% (650,000)
- African American/Black - 8% (515,000)
- Asian/Native Hawaiian/Pacific Islander - 7% (459,000)
- Multiple Race - 3% (180,000)
- American Indian/Alaska Native - 1% (80,000)

Patients who DO NOT receive a life-saving transplant

- African American/Black
- American Indian/Alaska Native
- Asian/Native Hawaiian/Pacific Islander
- Caucasian
- Hispanic/Latino

1 Numbers reflect U.S. recruitment activity as of October 1, 2007. Numbers, percentages and totals may not coincide due to rounding. Remainder of the Registry are unidentified.

2 Based on searches that did not proceed to transplant within 6 months. Some additional patients received their transplants later.
<table>
<thead>
<tr>
<th>Conditioning</th>
<th>Reduced Intensity</th>
<th>Matched Sibling Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Busulfan-fludarabine+ Alemtuzumab</td>
<td>Busulfan-Cyclophosphamide + ATG</td>
</tr>
<tr>
<td>Cell source:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matched sib marrow</td>
<td>8</td>
<td>144 (French experience)</td>
</tr>
<tr>
<td>Matched sib cord</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Unrelated cord</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Graft failure</td>
<td>4/8 with unrelated cords</td>
<td>3/144</td>
</tr>
<tr>
<td>Acute GVH II-IV</td>
<td>33%</td>
<td>23%</td>
</tr>
<tr>
<td>Chronic GVH</td>
<td>8.5%</td>
<td>9.6%</td>
</tr>
<tr>
<td>Overall survival</td>
<td>81.8%</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td>100% sibling donors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>62.5% umbilical cord donors</td>
<td></td>
</tr>
<tr>
<td>Event-free survival</td>
<td>77.8% (100% sibling donors, 50% umbilical cord donors)</td>
<td>92%</td>
</tr>
</tbody>
</table>
Animal Research in Gene Therapy

1. Mouse with sickle cell anemia, a disease that results in abnormal red blood cells.
2. A few skin cells are removed and cultured in a dish.
3. Skin cells are treated with viruses to turn them into induced pluripotent stem (iPS) cells, similar to embryonic stem cells.
4. The genetic mutation responsible for sickle cell disease is cut out and replaced with a normal snippet of DNA.
5. Corrected iPS cells are treated with another virus that causes them to become bone marrow cells.
6. Bone marrow cells are infused into the mouse that donated the skin cells. They settle permanently in the marrow and produce a constant supply of normal red blood cells, curing the mouse.