The Importance of Clinical Trials: Changing the Face of Sickle Cell Disease

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Sickle Cell Disease: Background

- Hemoglobinopathy (HbS) affecting 1 in 800 Black babies born in the United States
- Newborn screening detects approximately 2000 new cases each year
- Most common variants are HbSS, HbSβ-thal, HbSβ0, and HbSC
- Carriers (HbS-trait-FAS, FAC, FAE) are assumed asymptomatic; ratio of trait to SCD is 50:1
Sickle Cell Pathophysiology

- Vaso-occlusion can occur in any organ in the body
- Commonly affected organs include:
  - Spleen
  - Brain
  - Bone Marrow
  - Retina
  - Lungs
  - Kidney
  - Skin
The Story of Sickle Cell Disease

- 1910: Dr. James Herrick and his intern, Ernest Irons, described and linked clinical symptoms to abnormal hemoglobin, termed sickle cell anemia (in 1922)

- First patient: Walter Clement Noel, a 20 year old dental student from Granada studying at the University of Chicago
Sickle Cell Disease: Basic Research

Understanding of the genetics of sickle cell disease advanced from 1910 until the early 1980s, but no significant clinical advances

1910: Herrick provides description of sickle cells in symptomatic patient

1927: Hahn & Gillespie associate sickling with low oxygen concentration

1949: Linus Pauling publish: *Sickle Cell Anemia: A Molecular Disease in Science*. Cause of disease associated with change in protein structure

1956: Ingram & Hunt sequence hemoglobin and discover that the change of a single amino acid in protein sequence is cause of SCA

1978: Flavel prepares maps of the human beta and delta globin genes
Sickle Cell Research: A Brief History
The Comprehensive Sickle Cell Centers

- 1972: NIH/NHLBI established the Comprehensive Sickle Cell Centers (CSCC)
  - Presidential Initiative & Congressional mandate
  - NHLBI Sickle Cell Disease Advisory Committee mandated
  - Emphasis on
    - Basic research
    - Clinical care and research
    - Patient and Community Outreach
Finally: Clinical Studies with Patients

1982: Clinical Advances Start to Emerge

1982: Clinical observation of increase mortality due to overwhelming sepsis in children under 4 led to PROPS study (prophylactic penicillin). Study stopped early and prophylactic penicillin became the standard of care.

1984: Accidental cure discovered as child with SCA treated for leukemia with bone marrow transplant is cured of SCA

1985: Multicenter Study of Hydroxyurea stopped early because of clear benefits of HU for pain in adults with SCA

1995: Multicenter Study of Hydroxyurea stopped early because of clear benefits of HU for pain in adults with SCA

1996: CSSCD and STOP trials show 17% incidence of silent cerebral infarct and association between elevated cerebral vascular flow rate and stroke in children; chronic transfusion trial stopped early, became standard of care

2010: Chronic anemia linked to neurocognitive impairment in adults with SCD; transfusion trial started

2011: BABY HUG Trial Completed- hydroxyurea safe and demonstrates clinical significance for pain and other clinical symptoms in infants and toddlers
Sickle Cell Research: A Brief History
Outside the Centers

- Comprehensive Study of Sickle Cell Disease (CSSCD)
  - 1978-1998
  - 709 infants enrolled in natural history study
  - 1988: Brain Study started
  - 1994: Kidney, Psychosocial, MRA emphasized
  - CSSCD fundamentally changed understanding of critical clinical issues in SCD
    - Stroke and stroke onset
    - Mortality
    - Disease Severity
    - Pulmonary Issues
Cognitive Functioning in Children with Sickle Cell Disease
Cooperative Study of Sickle Cell Disease

1983: PROPS, PROPS II

- NHLBI funded multi-center study of prophylactic penicillin
- Stopped early because of definitive outcomes
- *Established prophylaxis as standard of care and led to SCD specific guidelines for later immunizations*
Stroke Prevention Trial in Sickle Cell Anemia (STOP)

- Multicenter study of Transcranial Doppler Ultrasonography (TCD) of cerebral arteries to predict stroke risk
- Children with vascular flow rates >200cm/sec randomized to chronic transfusion/no transfusion
- *Study stopped early because transfusion prevented subsequent stroke; Established TCD screening as standard of care.*
- *STOP II: Found transfusion must be continued*
Hydroxyurea

- Initially used in treatment of chronic leukemia
- Can lower WBC, needs to be monitored
- Mechanism: Hydroxyurea stimulates the production of Hemoglobin F (HbF), therefore reducing the concentration of HbS and the likelihood of sickling
Sickle Cell Research: A Brief History
Outside the Centers

- Multi-center Study of Hydroxyurea (MSH)
  - Opened in 1997
  - Adults with HbSS, ages 18-50 with at least 3 ED or hospitalizations for pain
  - Mechanism in SCD is increase in fetal hemoglobin (HbF) production that reduces HbS concentration and propensity to sickling
  - Study stopped prematurely because of significant results, established standard of care for prevention of pain in adolescents & adults
Sickle Cell Research: A Brief History Outside the Centers

Hydroxyurea Safety and Organ Toxicity

[HUSOFT] trial

- 21 infants in multi-center trial using liquid hydroxyurea
- Follow-up from 4 to 6 years
- Infants with SCA tolerate prolonged hydroxyurea therapy with sustained hematologic benefits, fewer ACS events, improved growth, and possibly preserved organ function.
- Established safety data for initiation of Baby HUG.
2001: Baby HUG

- Multi-center study of 200 infants (9-18 mos old at enrollment) randomized to hydroxyurea or placebo
- Primary outcomes: liver and splenic function
- Secondary: Neurodevelopment
- Results 2011: HU safe, had significant clinical benefits (Wang et al, The Lancet, 2011)
Sickle Cell Research: Ongoing Studies

Stroke With Transfusions Changing to Hydroxyurea (SWiTCH)
- Multi-center, randomized cross-over clinical trial
- 130 children 6-18 years with infarct treated with transfusion for at least 18 months

Outcomes
- Secondary stroke
- Management of iron overload
- Neurodevelopment
- Quality of life
Sickle Cell Research: Ongoing Studies

- Silent Infarction Transfusion Trial (SITT)
  - Multi-center, international study of chronic transfusion and prevention of silent infarct

- Neuropsychologic Function and Imaging in Adults with Sickle Cell Disease: A Pilot Transfusion Study
  - Multi-center study of 140 adults with HbSS (25-40 years old) with no history of neurologic disease who have hemoglobin < 9 gms
    - Significant differences with community controls on IQ
    - Cognitive function significantly associated with anemia
Hematopoietic Stem Cell Transplantation in Sickle Cell Disease

- Bone Marrow Transplant Clinical Research Network (BMT-CRN) established 2001
  - HSCT is the only known cure for SCD
  - Full and mixed chimerism approaches underway
  - 10% procedure-related mortality
  - Limited to patients with significant clinical conditions (e.g., stroke, repeated ACS)

- Sickle Cell Unrelated Transplant (SCURT)
  - Multi-center trial using unrelated donors to begin in 2009
Translation of Research to Clinical Practice: A Summary of Highlights

- Prevention of overwhelming bacterial sepsis through prophylaxis and immunization (PROPS)
- TCD Screening of Infants and Toddlers (STOP)
- Hydroxyurea for prevention of pain and other symptoms (MSH, HUSOFT)
- Oral chelators used to prevent iron overload
Sickle Cell Disease: Policy from Science

- Newborn screening legislation enacted in all 50 states, new standards of care
  - Prophylactic penicillin
  - Transcranial Dopper ultrasonography
  - Vaccinations for H-flu standard
Sickle Cell Disease: Policy from Science

- Quality-of-Care Indicators for Children With Sickle Cell Disease (Wang et al, 2011, Pediatrics)
  - Expert panel produces evidence-based quality of care indicators for treatment of children with sickle cell disease world wide
With All This Research, Where Are We?

- Management of acute pain has not changed substantially in more than a half century.
- Low incidence problems (e.g., leg ulcers, kidney disease, retinal disease) have seen no significant advances.
- Although more than 50% of children with SCA have neurocognitive deficits related to vascular, hypoxic, anemic, or pulmonary challenges, very few are identified for special services in the schools.
Why the Disconnect?

- While all 50 states have mandatory newborn screening for SCD, only a few have effective follow-up programs
- The Comprehensive Sickle Cell Centers provided outstanding service, but there were only 10 and they have not been geographically located near SCD population centers
- The Clinical Research Network only added 4 new centers to the CSCC network
Addressing the Clinical and Translational Research Needs in SCD is not Easy!

- Pediatric and adult emphases are different
  - Prevention vs. acute and chronic care focus
  - Underlying clinical infrastructure differs for children and adults
    - Adults over 21 often cannot be admitted to children’s hospitals
    - Severe and growing shortage of medicine hematologists

- Clinical revenue doesn’t sustain the clinical enterprise
Addressing the Clinical and Translational Research Needs in SCD is not Easy!

- Today, basic science supporting clinical and translational research in SCD is minimal
  - NIH budget for SCD-related basic research is substantially smaller than for other low incidence diseases
  - Pharmaceutical industry development of new orphan drugs has not been a priority, but that is changing
Addressing the Clinical and Translational Research Needs in SCD is not Easy!

- Numerous scientific clinical research challenges
  - Multiple organ involvement requires participation by many specialties that have not historically worked together
  - Clinical focus shifts across the lifespan
  - Meaningful endpoints of some clinical trials may take decades to determine
Addressing Clinical and Translational Research Needs in SCD is not Easy!

- Participant Concerns
  - Geographic access to a clinical research center
    Time, distance, travel expenses
  - Participant burden
    - Number of studies
    - Lifetime research participant?
  - Relevance of research to participant concerns
Other Critical Collaborations

- Community Based Organizations
  - Can play principal role as advocate for sickle cell
    - Research funding
    - Clinical care funding
  - Can legally advocate for sickle cell support at local, state, and federal level without compromising University legislative agendas
  - Can be major partner in participant recruitment for clinical trials and community support
Florida’s Challenges

- One of largest populations of children and adults with SCD in the United States
- CMS does excellent job with follow-up near pediatric centers, but some inevitably still don’t receive follow-up and standard of care
- Pediatric centers see more than 4000 children with SCD
- Adult care infrastructure is minimal
- Florida SCD mortality rate has historically been greater than national average
Florida’s Opportunities

- Florida pediatric centers have history of collaboration (e.g., FAPTP)
- Florida has the opportunity to be the “St. Jude or Dana Farber” of sickle cell disease
  - Lead consortium for Phase I and Phase II trials and innovation
  - Anchor for national clinical trials network
- Florida can improve implementation of clinical standards of care-Center of Excellence
What Do We Need to Do?

- Make clinical trials available
- Education the sickle cell community about the role clinical trials can play in improving how we treat and ultimately cure sickle cell disease
- Make it possible for those interested to participate
- Inform the community about what we learn
Final Consideration

- Clinical trials in childhood cancer have changed survival from 40% to more than 80%. Why can’t we do have the same impact for Sickle Cell Disease?
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