An Update on Clinical Trials in Sickle Cell Disease

24 September, 2016

Kevin Kuo, MD, MSc, FRCPC
Clinician-Investigator and Staff Hematologist
Red Blood Cell Disorders Program, Therapeutic Apheresis Program
Division of Medical Oncology and Hematology, University Health Network
Division of Hematology, Department of Medicine, University of Toronto

Conflict of Interest Disclosures

• Scientific advisory board: Agios
• Consultancy: Agios, Alexion, Novartis
• Honoraria: Alexion, Novartis
• Unrestricted education grant: ApoPharma
• Research collaboration: Phoenicia Biosciences
• Discussion of ACE-536 and AG-348
Objectives

• Review the history of thalassemia management and it's association with iron chelation

• Discuss the obstacles to thalassemia management in the context of the current paradigm

• Examine possible non-chelating means of managing iron overload

• Explore the possibility of pharmacologic means to achieve transfusion-independence in transfusion-dependent thalassemia

Treatment - Where We Were

- 1970: Penicillin prophylaxis
- 1980: Pneumococcal vaccine
- 1990: Hydroxyurea
- 2000: TCD
- 2010: SIT, SWiITCH, STOP, STOP2
Where We Were


Morbidity of SCD and Rationale for Curative Treatment

<table>
<thead>
<tr>
<th>Organ Damage</th>
<th>% Affected</th>
<th>Median Age of Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gall bladder disease</td>
<td>28%</td>
<td>28 yrs</td>
</tr>
<tr>
<td>Avascular necrosis</td>
<td>21%</td>
<td>30 yrs</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>15%</td>
<td>32 yrs</td>
</tr>
<tr>
<td>Leg ulcer</td>
<td>14%</td>
<td>32 yrs</td>
</tr>
<tr>
<td>Priapism</td>
<td>13%</td>
<td>31 yrs</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>11%</td>
<td>37 yrs</td>
</tr>
<tr>
<td>CVA</td>
<td>11%</td>
<td>21 yrs</td>
</tr>
<tr>
<td>Proliferative retinopathy</td>
<td>14-35%</td>
<td>24 yrs</td>
</tr>
<tr>
<td>Silent brain infarct</td>
<td>35%</td>
<td>14 yrs</td>
</tr>
</tbody>
</table>

Kauf et al., AJH 2009
Not Many Options Despite Advances

- Evidence-based treatment options?
  - Yes: Follow evidence-based options
    - Transfusions
    - Hydroxyurea
    - "Supportive care"
  - No: Hydroxyurea

- Clinical Improvement?
  - Yes: Continue Tx
  - No: Transfusion

- Clinical Trials? Bone Marrow Transplant?

How long does it take to develop a drug? Example: hydroxyurea

- Phase III
  - MSH trial [16]
- Phase I/II trial in children (HUG-KIDS) [21,23,24]
- SWITCH trial enrollment begins
- Prevention of organ damage [48-54,57,59]
- 1984
- 1992
- 1995
- 1997
- 1999
- 2001
- 2003
- 2004
- 2005
- 2006
- 2007
- 2008
- 2009
- 2010

- Prevention of secondary CVA [58]
- BABY HUG enrollment begins
- HUSOFT extension [28]
- BABY HUG Results
- TWINCH trial begins
- Lowering TCD velocities [55,56]
- Follow-up to MSH [29]
- Short-term pediatric efficacy [17-20]
- Phase 1/II trial in adults [15]
Mapping Out Potential Targets

- HbS
- HbF

Sickling

Hemolysis

Free Heme

NO depletion \( \downarrow \) synthesis

ROS generation

\( \text{H}_2\text{O}_2 \)

Platelet activation

Vaso-constriction

Vaso-occlusion

I-CAM, P-selectin, E-selectin, TLR4

Platelet activation

Vaso-constriction

\( \text{cGMP} \leftarrow \text{GTP} \)

\( \text{L-Arg} \)

L-Arginine

Orn

\( \text{NO} \)

\( \text{O}_2^* \)

\( \text{H}_2\text{O}_2 \)

Free Heme

Hemolysis

\( \text{ROS} \)

\( \text{O}_2^* \)

\( \text{H}_2\text{O}_2 \)

Vaso-occlusion

I-CAM, P-selectin, E-selectin, TLR4

Platelet activation

Vaso-constriction

\( \text{cGMP} \leftarrow \text{GTP} \)

\( \text{L-Arg} \)

L-Arginine

Orn

\( \text{NO} \)

\( \text{O}_2^* \)

\( \text{H}_2\text{O}_2 \)

Fetal Hemoglobin Induction

- DNA demethylating agents:
  - 5-Azagycidine
  - Decitabine
- Histone deacetylase (HDAC) inhibitors
  - Vorinostat
  - Panobinostat
- Short-chain fatty acid derivatives
  - 2,2-dimethylbutyrate (HQK-1001)
- Thalidomide derivatives
  - Pomalidomide
- LSD-1 inhibitors
- Stress signaling enhancer
DNA Demethylating Agents

- DNA demethylation → expression of silent γ globin genes
- 5-Azacytidine
  - IV, low dose intermittent regimen
  - Phase 2 (Saunthararajah et al., 2003)
  - Myelosuppressive
  - Mutagenic potential
- Decitabine + tetrahydouridine (THU)
  - po (THU inhibits metabolizing enzyme of Decitabine)
  - Phase I (NCT01685515) adult, completion in Dec 2014
  - Phase II (NCT01375608) adult, recruiting

Saunthararajah Y et al., Blood. 2003 Dec 1;102(12):3865-70

Histone Deacetylase (HDAC) Inhibitors

- Inhibit decetylation → expression of silent genes
- 2,2-dimethylbutyrate (HQK-1001)
  - Phase II (Reid 2014), double-blind, placebo-controlled
  - No significant increase in HbF (0.9%)
  - Nausea, vomiting
- Vorinostat
  - Phase II (NCT01000155), adult, recruiting
- Panobinostat (LBH589)
  - Phase I (NCT01245179)

Thalidomide Derivatives

- anti-VEGF, anti-inflammatory, anti-proliferative, immunomodulatory (anti-TNFα)
- Restore erythropoiesis and reduce or eliminate blood transfusion dependency in MM and MDS
- Upregulate $\gamma^G$ and $\gamma^A$ gene transcription
- Pomalidomide
  - Phase I (NCT01522547), N=15 SCD patients

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Dx</th>
<th>Dose (mg)</th>
<th>Duration</th>
<th>Hb (g/dl)</th>
<th>HbF (%)</th>
<th>F-cells (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>Final</td>
<td>Baseline</td>
<td>Final</td>
<td>Baseline</td>
</tr>
<tr>
<td>52/M</td>
<td>SS</td>
<td>4</td>
<td>70 days</td>
<td>9.4</td>
<td>9.8</td>
<td>10.7</td>
</tr>
<tr>
<td>20/M</td>
<td>SS</td>
<td>4</td>
<td>84 days</td>
<td>8.6</td>
<td>11.4</td>
<td>7.1</td>
</tr>
<tr>
<td>27/M</td>
<td>SS</td>
<td>4</td>
<td>84 days</td>
<td>10.6</td>
<td>11.3</td>
<td>20.9</td>
</tr>
<tr>
<td>50/M</td>
<td>SS</td>
<td>3</td>
<td>460 days</td>
<td>10.6</td>
<td>11.9</td>
<td>14.8</td>
</tr>
</tbody>
</table>


Anti-Sickling Agents

- $O_2$ affinity modifier
  - GBT440 (GTx011)
- Alpha-globin binder
  - 5-hydroxymethylfurfural, 5-HMF (Aes-103)
- Activin inhibitor
  - ACE-536
- Adenosine A2B Receptor Antagonists
  - PAB1115
**O$_2$ affinity modifier**

Source: Global Blood Therapeutics

---

**GBT440 Phase 1 in SCD patients**

Source: Global Blood Therapeutics
Alpha Globin Binder

- 5-hydroxymethylfurfural, 5-HMF (AES-103)
- Binds to hemoglobin α subunit, increases O₂ affinity, stabilizes the R-state
- Inhibits hypoxia-induced sickling
- In vitro study:
  - Reduces sickle fiber formation
  - Reduced erythrocyte fragility under shear stress
  - Reduced hypoxia-induced hemolysis
- Phase II (NCT01987908) adult, recruiting
  - Outcomes: Safety, Hb, , PK, PD, LDHm SpO2%, p50, pain, exercise tolerance


Activin Inhibition

- Luspatercept (ACE-536)
- In SCD transgenic mice model:
  - Reduced hemolysis and ROS, Increase RBC
  - 3-fold decrease in irreversibly sickled cells
- Phase I (Attie et al. 2014)
  - N=32, healthy volunteers, completed
  - 83% had Hb increase > 10 g/L
  - No SAE, injection site irritation, rash

http://www.nature.com/nm/journal/v20/n4/images/nm.3524-F1.jpg
Cell Adhesion Inhibitors

- Sickle cell mice lacking P-/E-selectins protected from vaso-occlusive crises
- P-selectin inhibitor
  - Pentosan polysulfate
  - Sel-G1 (anti-P-selectin monoclonal antibody)
- E-selectin inhibitor
  - GMI-1070
- Membrane adhesion blocker
  - Purified poloxamer (MST-188)
- TLR4 Inhibitor
  - TAK-242

Pentosan Polysulfate

- P-selectin inhibition
- Phase: I/II (Kutlar 2012)
  - Daily dosing
  - Study discontinued due to economic reasons
  - No significant change in pain score (?) Underdose


Pan-selectin Inhibitor

- GMI-1070 (Rivipansel), pan-selectin inhibition
- Phase 1: (Wun 2014) 15 adult SCD patients not in VOC
- Phase 2: 42 SCD patients in VOC
  - Double-blind, placebo-controlled
  - IV q12h up to 7 days, start < 24 hours of 1st dose of IV opioids
  - Time to resolution of VOC was lower but not statistically significant
  - Pooled safety data: headache (16-25%), dizziness (3-9%), infusion site reaction (5-9%)
- Phase 3 (NCT02187003) will commence soon
  - Double-blind, placebo-controlled RCT
  - Outcomes: Time to discharge, readiness-for-discharge, IV opioid consumption, time IV opioids discontinuation, 3 days re-hospitalization rate for VOC, PRO (pain and function)

Membrane Adhesion Blocker

- MST-188 (purified poloxamer 188)
- Non-ionic surfactant, improves microvascular flow
- Previous phase III with non-purified poloxamer 188, N = 126
  - Mean duration of painful episodes was decreased (133 vs 141 hours, \( p=0.04 \)).
  - More pronounced effect in
    - Age < 15 (mean difference 21 hours, \( p=0.01 \))
    - Patients receiving HU (mean difference 16 hours, \( p=0.02 \))
  - Proportion of patients achieving crisis resolution increased
    (65/126 (52%) vs. 45/123 (37%); \( p=0.02 \))
  - No significant reduction in hospital LOS
- Moderately severe increase in creatinine in subjects with acute MI on separate study
- New phase III: purified poloxamer 188 developed to address previous AE

TLR4 Inhibitor

- TAK-242 (Resatorvid)
- Inhibition of heme-induced P-selectin and vWF expression via TLR4 pathway
- In sickle mice:
  - Reduces leukocyte rolling and adhesion
  - Inhibits NF-\( \kappa \)B activation
  - Prevents heme-induced lethality
  - Inhibits heme-induced neutrophil extracellular trap formation
- No human studies yet
Inflammatory Inhibitors

- CO mediated inhibition
  - MP4CO
- iNKT inhibitor
  - NKTT-120
  - Regadenoson
- Platelet inhibitors
  - Abxicimab
  - Prasugrel
- Inhibition of endothelial TF expression
  - Statins
CO-mediated inhibition

- CO and HO-1 expression inhibit oxidative stress, inflammation and microvascular occlusion via TLR4
- CO may also inhibit S polymerization
- MP4CO
  - PEGylated human Hb saturated with CO
  - Upregulation of HO-1 and Nrf2 expression
  - Downregulation of I-CAM, V-CAM, NF-κB
  - Effects on Nrf2 activation
  - Decreased P-selectin and vWF on pulmonary vascular cells
  - $O_2$ delivery to ischemic tissues

MP4CO

- Phase 1b (Howard 2013)
- Double-blind, comparator controlled, dose escalating
- 3:1 randomization
- Common AEs: headaches (mild and transient), dizziness, fatigue
- No SAEs
- Unable to proceed to phase 2 due to lack of funding
iNKT inhibitor

- TCR activates iNKT and in turn upregulates cAMP
- cAMP inhibits NFkB which will downregulate cytokines and inflammation
- NKTT-120 inhibits TCR which activates iNKT
- Regadenoson activates A2AR which activate iNKT

Restoration of NO
Nitric Oxide Donors

• Topical sodium nitrite
• Potent vaso-dilator and anti-inflammatory
• Restores NO milieu in the vasculature
• Treatment of sickle cell leg ulcers
• Phase 2 study at NHLBI, NIH
  • q 2 days application x2 then 2x/week x 4 weeks
  • MRI, infrared photography, thermo-patch application, blood flow, pain and QoL assessment weekly x 5 weeks
  • Study ongoing

Characteristics of Leg Ulcers at the RBCD Clinic

• N = 22 (5%)
• 13 (59%) active ulcers
• 9 (41%) inactive ulcers
PROPRIETARY ACTIVATION PROCESS

- A primary dressing layer comprising a polypropylene mesh impregnated with 1M sodium nitrite solution.
- A proprietary sheet hydrogel dressing which comprises carboxylic acid groups co-polymerised into the cross-linked anionic polymer
- Creates an environment of pH 4.2-4.5 which can support the sustained creation of nitric oxide and equilibrium in the presence of a nitrite source

Upon combination the aqueous, acidified environment beneath the hydrogel promotes the sustained creation, adsorption and release of nitric oxide within the hydrogel.

PRO-NOx HEALING TRAJECTORY

In a multi-centre clinical study for DFU PRO-NOx achieves more in 4 weeks than SOC achieves in 12 weeks

PRO-NOx achieved a median wound area reduction of 97%

P Value 0.0044 (Mann Whitney)
Summary

- Only 7% of candidate compounds in pre-clinical phase are successful in phase III studies
- What makes sense mechanistically may not translate into meaningful clinical benefit
- Effect size may not be as pronounced as animal models
- Future trials must have clinically relevant endpoints
  - Functional outcomes
  - QoL measures
  - Composite endpoints
- Focus on prevention vs. treatment
- Multi-agent regimen, similar to chemotherapy, may be necessary to target multiple pathways of the sickling process

High-risk, high-reward therapies

Stem cell transplant and Gene therapy
Hematopoietic Stem Cell Transplant (HSCT) in SCD

- First transplant in 1984
  - recipient: SS + AML, donor: AS
- 1,200 transplanted in Europe and US, mostly children
- HLA-identical sibling HSCT
  - Excellent survival to adulthood in children
  - Considered standard of care for children and adults
  - Reduced-intensity regimens to minimize toxicity in adults
  - (Gluckman Hematology 2013)
- Matched unrelated donor and haploidentical HSCT are currently performed in research setting
- Field is advancing rapidly

Largest Studies on MRD HSCT in SCD

(Gluckman Hematology 2013)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor</td>
<td>HLA-Id Sib</td>
<td>HLA-Id Sib</td>
<td>HLA-Id Sib</td>
<td>HLA-Id Sib</td>
<td>HLA-Id Sib</td>
<td>HLA-Id Sib</td>
</tr>
<tr>
<td>N</td>
<td>50</td>
<td>50</td>
<td>185</td>
<td>67</td>
<td>10</td>
<td>389</td>
</tr>
<tr>
<td>Conditioning (mg/kg)</td>
<td>BU 16 CY 200 TU</td>
<td>BU 14 CY 200 Anti-CD52 or ATG</td>
<td>BU 16 CY 200</td>
<td>BU 16 CY 200</td>
<td>TBI 3Gy Anti-CD52</td>
<td>BU/CY (89%) ATG (67%)</td>
</tr>
<tr>
<td>GVHD prophylaxis</td>
<td>ATG, CsA</td>
<td>CsA, MTX</td>
<td>CsA, MTX</td>
<td>CsA, MTX</td>
<td>Sirolimus</td>
<td>CsA (98%)</td>
</tr>
<tr>
<td>Median follow-up, mo</td>
<td>60</td>
<td>38</td>
<td>72</td>
<td>61</td>
<td>30</td>
<td>72</td>
</tr>
<tr>
<td>EFS</td>
<td>82%</td>
<td>84%</td>
<td>91%</td>
<td>85%</td>
<td>90%</td>
<td>88%</td>
</tr>
<tr>
<td>OS</td>
<td>96%</td>
<td>94%</td>
<td>96%</td>
<td>96%</td>
<td>100%</td>
<td>95%</td>
</tr>
<tr>
<td>Rejection</td>
<td>10%</td>
<td>10%</td>
<td>7%</td>
<td>n 9</td>
<td>0%</td>
<td>n 6</td>
</tr>
<tr>
<td>TRM</td>
<td>7%</td>
<td>6%</td>
<td>7%</td>
<td>0%</td>
<td>0%</td>
<td>n 18</td>
</tr>
<tr>
<td>aGVHD II</td>
<td>20%</td>
<td>15%</td>
<td>20%</td>
<td>10%</td>
<td>0%</td>
<td>21%</td>
</tr>
<tr>
<td>cGVHD</td>
<td>20%</td>
<td>12%</td>
<td>14%</td>
<td>22%</td>
<td>0%</td>
<td>12%</td>
</tr>
</tbody>
</table>

Id Sib, identical sibling; MAC, myeloablative conditioning; NMA, non-myeloablative conditioning; TLI, total lymphoid irradiation; MTX, methotrexate; Tacrolimus; MMF, mycophenolate mofetil; DFS, disease-free survival; aGVHD, acute GVHD; and cGVHD, chronic GVHD.
Registry Data of HSCT in SCD
(Gluckman Hematology 2013)

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>611</td>
</tr>
<tr>
<td>Type of donor</td>
<td></td>
</tr>
<tr>
<td>HLA-identical</td>
<td>487</td>
</tr>
<tr>
<td>CB related and unrelated</td>
<td>73</td>
</tr>
<tr>
<td>Haploidentical donor</td>
<td>34</td>
</tr>
<tr>
<td>Other unrelated donor</td>
<td>17</td>
</tr>
<tr>
<td>OS</td>
<td></td>
</tr>
<tr>
<td>1 y</td>
<td>95% 1%</td>
</tr>
<tr>
<td>2 y</td>
<td>94% 1%</td>
</tr>
</tbody>
</table>

HSCT in SCD Children

- Event free survival 80 to 90%
- Graft rejection
- Graft-versus-host disease
- Infertility
- Infection
- Veno-occlusive disease of the liver
- Death from transplant related complications
Hematopoietic Cell Transplantation for Young Adults with Severe Sickle Cell Disease
BMT CTN 1503
Dr. N. Krishnamurti et al.
STRIDE 2 team

R34 NHLBI-funded Pilot Trial

- Objective: to determine the safety of HCT in patients aged 15-40 years with severe SCD defined as 1-year disease-free survival ≥75%
- Trial period: 10/2012 – 06/2015; 8 centers
- Median age 22 years
- Donors: 17 HLA-matched sibling; 5 HLA-matched URD
- Results (for N = 22)
  - N = 21 alive; median follow-up: 9.7 months
  - OS 95% (90% CI 76%; 99%)

Courtesy of Krishnamurti L, et al. BMT CTN 1503
R34 NHLBI-funded Pilot Trial

- No graft failure
- High level of full donor and erythroid chimerism by 6-months; partial lymphoid chimerism
- N = 2 acute GVHD
- N = 3 chronic GVHD
- N= 6 grade 4-5 SAEs in 4 patients
- N = 1 dead (cause of death: PRES/intracranial bleed)
  - PRES = posterior reversible leukoencephalopathy

Study Design - BMT CTN 1503

Consultation with HCT physician

Clinically Eligible: Consent Register in AdvantageEDC™

ERG: Confirm Clinical Eligibility

HLA typing Re-register in AdvantageEDC™ for Biologic Assignment

Not Eligible

Off study

Comparison Cohort vs.

HCT not Performed

HCT

Donor

HCT

Courtesy of Krishnamurti L, et al. BMT CTN 1503
Eligibility Criteria – BMT CTN 1503

• Age 15 – 40 years
• CNS event: stroke or deficit lasting >24 hours
• ≥ 2 episodes of acute chest syndrome (ACS) in preceding 2 years despite adequate supportive care measures
• ≥ 3 episodes of pain crisis (VOC) in preceding 2 years despite adequate supportive care measures
• ≥ 8 transfusions per year for ≥ 1 year to prevent SCD-related complications (VOC, ACS, stroke)
• Tricuspid valve regurgitant jet (TRJ) ≥ 2.7 m/sec

Primary Endpoint – BMT CTN 1503

• Primary endpoint: estimate of overall survival at 2-years after biologic assignment
  • We will compare the survival rates at two years, with the goal of establishing that the difference in the proportion surviving is no more than 0.15 lower in the donor arm
  • Analyze according to assigned groups
Secondary Endpoints – BMT CTN 1503

- Changes in record-based assessments of sickle-related events (baseline and at 2-years)
  - Pulmonary: pulmonary hypertension measured as TRV ≥ 2.7 m/second or oxygen saturation <92%
  - Cerebrovascular: stroke, transient ischemic event, seizure
  - Renal: albuminuria or creatinine >1
  - AVN hip or shoulder
  - Leg ulcers
- Exact logistic regression will be used to estimate an odds ratio of such events

Courtesy of Krishnamurti L, et al. BMT CTN 1503

Secondary Endpoints – BMT CTN 1503

- Functional endpoints
  - Health-related quality of life (HRQoL) collected via PROMIS57
  - Mean pain intensity captured via e-diary, BID, on over a 28-day period
  - 6-minute Walk Distance Test (6MWD)
- Focus on changes from baseline to 2-years
  - No imputation for missing data

Courtesy of Krishnamurti L, et al. BMT CTN 1503
Risk of HSCT in adults

- Side effects of chemotherapy (e.g. nausea, vomiting, diarrhea, mouthsores, serious infections)
- Infertility
- Graft versus host disease 10 to 20%
  - Skin, Gastrointestinal tract, Liver, Lungs, Eyes
- Veno-occlusive disease
- Posterior reversible encephalopathy (PRES) < 5%
- Therapy related malignancies
- Death
- Risk increases with age

Gene Therapy in Hemoglobinopathies

- Correction of defective globin gene in autologous HSC via recombinant approaches
- Challenges:
  - Requires massive hemoglobin production in a lineage specific manner
  - Lack of selective advantage for corrected hematopoietic stem cells
- Two promising approaches
- Lentiviral vectors (12 βTM, 2 SCD)
- CRISPR/Cas9
**Lentiviral β^{A-T87Q}-Globin Vector**

- The modified lentiviral vector is replication defective, self-inactivating
- β^{A-T87Q}-globin
- Mutation derives from γ-globin
- Interrupts polymerization of β^{S}

Kanter J ASH 2015 Abstract 3233

**O2 Dissociation Curve of β^{A-T87Q}**

HGB-204/5/6 Study Schema

HGB-204 (βTM) Study

- 11:2 F:M
- Median age 21
- 6 β0/β0, 4 βE/β0
- β+/β+, β+/β0, βx/β0
- pRBC transfusion requirement: 14 mL/kg/month
- 3 SAEs: CVC thrombosis, skin infection, liver VOD
- 9 stomatitis, 7 febrile neutropenia, 4 pharyngeal inflammation, 2 irregular menses

Walters MC, et al. ASH 2015 Abstract 201
HGB-204 (βTM) Study Results

- $\beta^0/\beta^0$: reduction in transfusion requirement
- 33%, 52%, 47%, 1 patient transfusion independent
- $\beta^{\text{non}-0}/\beta^0$: achieved transfusion independence

Walters MC, et al. ASH 2015 Abstract 201

HGB-205 Study

- Subject 1204: SCD
- Frequent VOC despite HU x 7 years
- Improvement with pRBC transfusion since 2010
- ACS x2
- Bilateral AVN
- Splenectomy
- Outcome after 1 year:
  - Off transfusion in Day+88
  - No hospitalization for SCD-related events
  - Retic 238 → 143, LDH 626 → 274

HGB-206 (Severe SCD)

- Patient characteristics:
  - 8 Recurrent VOC
  - 7 ACS
  - 1 overt stroke
  - 3 TRJV > 2.5 m/s
- 1 SAE pain from bone marrow harvest
- 3 SAEs post-infusion: 1 bacteremia, 2 VOC
- 9 other AEs: fever, mouth pain, mucositis, febrile neutropenia, anorexia, fatigue, dyspnea, bacteremia

Kanter J ASH 2015 Abstract 3233

Advantages of Gene Therapy over HSCT

- Graft rejection
- GvHD
- Transplant-related complications
- Risks increase with age
- Increasing disease-related morbidity with age
- Infertility
- Therapy-related malignancies
- Donor availability
  - survival MRD > MUD > UD > Haplo
- Cost
The Problem

- The adolescent young adult (AYA) population (ages 16 to 25) with chronic disease is vulnerable to worsened health outcomes
  - Shift from a paternalistic to an independent environment
  - Emergence of psychosocial issues (e.g. depression)
  - High rates of school/work absences (38.4 missed school days/year in SCD patients)
  - Loss of follow up
  - High rates of hospitalizations
  - Worsened morbidity (development of chronic complications)
  - High mortality (7 fold increase relative to other SCD age groups)

Blinder et al., 2013; Boulet et al., 2010; Okumura et al., 2010

Root causes of the problem

- Transition in care is a life-changing and continuous process
- Quality of care decreases from pediatric to adult care
- Disengagement from the health care system
- Decrease in preventative and screening visits
Question

• Does a comprehensive transition program with dedicated transition coordinator reduce lost to follow-up, improve medication adherence and appointment attendance, and reduce rate of hospitalization in sickle cell disease and thalassemia adolescents and young adults?

Comprehensive transition program with dedicated transition coordinator reduced lost to follow-up and improved medication adherence in sickle cell disease and thalassemia adolescents and young adults

Brooke Allemang, BHSc, MSW, Kate Allan, MSW, Colleen Johnson, BScN, MN/NP, Melina Cheong, BScN, MN/NP, Patrina Cheung, BSc, Isaac Odame, MBChB, FRCPath, FRCPC, Richard Ward, MSc, MRCP, FRCPath, Suzan Williams, MD, MSc, FRCPC & Kevin Kuo, MD, MSc, FRCPC
Patients that met criteria for transition

Lost to follow-up between age 12 and 18

Died prior to transition

Lost to follow-up between pediatric and adult center

Transferred or transitioned to adult center

Transfer

- 51
- 9
- 2
- 2
- 38

Transition

- 61
- 3
- 0
- 1
- 57

- 11 patients were lost to follow-up in the transfer process while only 4 were lost to follow-up in the transition program (P = 0.0335)

Medication Adherence

- Patients in the Transition Cohort were significantly more likely to maintain or improve adherence to ≥4/7 days/week

![Graph showing medication adherence comparison between Transfer Cohort and Transition Cohort](Courtesy of Allan K. MSW, RSW)
Appointment Attendance

- Patients in the Transition Cohort were more likely to maintain or improve attendance to ≥ 90%

![Bar chart showing appointment attendance](chart)

- **p = 0.096, OR = 2.254**

Hospitalization

- Participation in the structured transition program did not predict difference in frequency of hospitalizations (**p=0.231**)

- No demographic variables independently predicted frequency of hospitalizations in this sample (**p=0.985**)

![Hospitalization chart](chart)