Gene Therapy Collaborative:
“Leadership Team Development: Feasibility of hemophilia gene therapy at the CU HTC”

LITeS 06May2022

Michael Wang, MD  Angela Blue, MBA  Desiree Hill, PharmD  Kathryn Hoeft, RN, BSN, MSHSA  Steven Powell, MBA

University of Colorado Hemophilia & Thrombosis Center

We Create Hope.
Team members:

- Mike Wang: HTC Co-Director, HTC PI for gene therapy clinical trials
- Angie Blue: HTC Program Manager
- Desi Hill: HTC Pharmacy Manager
- Kate Hoeft: HTC Clinic Manager
- Steve Powell: HTC Finance Manager

Each team member plays a critical role in developing any new therapeutic area within the CU HTC Clinic.
Setting the stage: Gene therapy for hemophilia

Cell Phones and Landlines: *The Impact of Gene Therapy on the Cost and Availability of Treatment for Hemophilia*

*Katherine A High, Mark W Skinner*

Molecular Therapy 2011:19(10);1759-60.

“Putting spontaneity back in life.”
“Patients are preconditioned to what they can and cannot do.”

*Mark Skinner, Past President WFH*

Hemophilia Overview

- **Monogenetic** disease caused by mutations in genes encoding coagulation factors VIII (Xq28) and IX (Xq27.1-27.2)
- Not a founder effect; 2931 mutations reported for FVIII; 1133 for FIX (cdc.gov/hemophiliamutations)

Clinical manifestations:

- Skin
- ICH
- Soft tissue & Muscle
- Joint
- Arthropathy
- Chronic Pain/Surgery

Complications of therapy:

- Inhibitors
- IV Access
- Tx Fatigue/adherence
- Cost

$5-700,000/yr for an adolescent

*Peyvandi F, NEJM 2016;374:205.*
Advances in Hemophilia Care

1900-1990:
- 1940: Pre-Bld Tx Life Expectancy- Teens
- 1964: Judith Graham Pool discovers Cryo
- 1975: Carol Kasper 1st Inhibitor Assay
- 1982: 1st linkage of HIV to plasma conc
- 1984: FVIII gene sequenced
- 1992: 1st recombinant FVIII licensed
- 1999: 1st gene Tx trial started
- 2007: RCT proves efficacy of prophylaxis
- 2014: 1st Ext T1/2 Factor
- 2017: 1st Non-Factor Product

References:
- CSL Behring; idealvion.com
- Manco-Johnson MJ. NEJM 2007;357.
Current therapeutic landscape for hemophilia
There are many options for hemophilia patients

Factor replacement therapies (green), Gene or Cellular therapies (red), substitutive therapies (purple), rebalancing therapies (blue)

VWD Type 3

Croteau, Wang & Wheeler. AJH (2021)
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Half-Life (12h) factor prophylaxis</td>
<td>Peaks for sports and activities</td>
<td>Efficacy Inadequate: decreased but persistent joint disease; Frequent Venipuncture; Adherence Suboptimal</td>
</tr>
<tr>
<td>Extended half-life factor prophylaxis</td>
<td>2-4 injections per month Better adherence</td>
<td>Long trough level</td>
</tr>
<tr>
<td>Non-factor bypassing agent</td>
<td>Constant hemostatic activity and no trough; Subcutaneous administration</td>
<td>No peaks for sports; procedures with only 10-30% hemostasis; still have bleeding</td>
</tr>
<tr>
<td>Gene therapy</td>
<td>One time treatment (?)</td>
<td>Inconsistent dose-response; Unknown durability; Unknown long-term toxicity</td>
</tr>
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</table>
Gene therapy 2022: Hemophilia

Somatic gene addition using Adeno-Associated Virus

Delivery to target tissue

Transduction
Episomal Transgene

Capssid tropism

Protein
Synthesis

Factor VIII

Hepatocyte

Episomal transgene

Uncoating
Endosomal escape

Promotor, regulatory elements, transgene, codon optimization

Courtesy of Lindsey George, MD; THSNA 2018
Hemophilia gene therapy:
Ushering in a new treatment paradigm?

Knowns
- Short-term safety
- Evidence of Preliminary Efficacy
- High titer, multi-serotype cross-reactive AAV NAb development post AAV vector

Unknowns
- Durability of expression & expression variability
- Desired therapeutic window & assay measurement predictability of in vivo hemostasis
- AAV NAb assays: clinical correlate and assay standardization
- Long term safety & genotoxicity risk

Lindsey A. George, Hematology Am Soc Hematol Educ Program, 2021, Figure 4.
Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A

PHASE 3, OPEN-LABEL, SINGLE-GROUP STUDY

134 Adult men with severe hemophilia A (factor VIII activity ≤1 IU/dl)

Change in Factor VIII Activity
Mean increase, 41.9 IU/dl (95% CI, 34.1 to 49.7); P<0.001

Treated Bleeding Episodes
Mean change, −4.1

Factor VIII Infusions
Mean change, −133.9

Valoctocogene roxaparvovec significantly increased factor VIII activity and reduced bleeding and factor VIII use; 16.4% of patients had serious adverse events.

M.C. Ozelo et al. 10.1056/NEJMoa2113708

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Reality for patients with hemophilia A & B

Gene therapy will be approved
  • FVIII and FIX GT were submitted to the FDA in March 2022 (fast track)
  • Dominant “model” for infusion is for a limited number of HTCs to be “chosen” and patients will travel to them
  • Genotoxicity concerns are surfacing (NIH conference focused on AAV toxicity)

Patients will want it, though not all patients are appropriate for it
  • Limited pool of eligible patients

Gene therapy has multiple acute and down stream economic outcomes for patients and HTCs
  • Factor sales fund HTC clinic care and in-part clinical research

HTCs will need to add a new care model to incorporate into clinical work-flow
  • HIV/AIDS, hepatitis B/C changed care but was limited
Desired Outcome(s) for GTC LITeS Project

1. Start 2022 with a refreshed Mission, Vision & Values of the HTC
   a. All projects will be Mission driven

2. Create a comprehensive picture of “What We Are Getting Into”
   a. Pharmacy requirements
   b. Clinical safety requirements
   c. Financial metrics and models
   d. Standards of patient care
   e. Campus & regional collaboration models
      i. Create of new analytical process to look “forward” when planning for change (MOU, staffing, finance, …)

3. Create detailed, realistic, mutually acknowledged processes & plans
   a. Clinical protocols of Inclusion/Exclusion, Patient education manual, Staff education presentation(s), Clinical Care Guideline, Pharmacy manual, Financial tool(s), Marketing/Branding

4. Present our work in May 2022 and gather CUAMC feedback and evaluation of resources and other programs/collaborations to move forward with CUAMC recognition and support
Hemophilia gene therapy in the context of the patient journey

Michael Wang, Claude Negrier, Frank Driessler, Clifford Goodman, Mark Skinner

(in press)
**Local assessment of gene therapy interest**

**Patient interest in receiving gene therapy at CU HTC**
- Patients 18 years and older: Severe hemophilia A or B without inhibitor
- Current treatment: on demand or prophylaxis
- Age range 18-73 years (median 33 years; mean 34.7)
- *If eligible and approved tomorrow, when would you like to receive gene therapy?*

<table>
<thead>
<tr>
<th></th>
<th>HA Prophy</th>
<th>HA OD</th>
<th>HB Prophy</th>
<th>HB OD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within the next year</td>
<td>6 (38%)</td>
<td>1 (6%)</td>
<td>4 (66%)</td>
<td></td>
<td>11 (50%)</td>
</tr>
<tr>
<td>In 1-5 years</td>
<td>4 (25%)</td>
<td></td>
<td>(2)*</td>
<td></td>
<td>4 (18%)*</td>
</tr>
<tr>
<td>Not sure</td>
<td>4 (25%)</td>
<td></td>
<td>1 (17%)</td>
<td></td>
<td>5 (23%)</td>
</tr>
<tr>
<td>Never</td>
<td>1 (6%)</td>
<td></td>
<td></td>
<td>1 (17%)</td>
<td>2 (9%)</td>
</tr>
</tbody>
</table>
Regional assessment of gene therapy interest

Patient interest in receiving gene therapy at CU, OHSU & WACBD (>60 patients)

- Patients 18 years and older: Severe hemophilia A or B without inhibitor
- Current treatment: on demand or prophylaxis
- *If eligible and approved tomorrow, when would you like to receive gene therapy?*

<table>
<thead>
<tr>
<th></th>
<th>CU</th>
<th>OHSU</th>
<th>WACBD</th>
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<tbody>
<tr>
<td>Within the next year</td>
<td>50%</td>
<td>25%</td>
<td>30%</td>
</tr>
<tr>
<td>In 1-5 years</td>
<td>18%</td>
<td>50%</td>
<td>45%</td>
</tr>
<tr>
<td>Not sure</td>
<td>23%</td>
<td>---</td>
<td>15%</td>
</tr>
<tr>
<td>Never</td>
<td>9%</td>
<td>25%</td>
<td>10%</td>
</tr>
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</table>
CU HTC gene therapy experience:
Local assessment of “eligibility”

• FVIII
  • BioMarin: phase 3
  • Takeda (cancelled prior to phase 3 enrollment)
    • Participated in AAV prevalence study

• FIX
  • uniQure: phase 3
  • Pfizer (Spark): phase 3
Gene therapy eligibility: phase 3 protocols (4)

Inclusion

1. Male (female???)
2. Age ≥18 years
3. Subjects with congenital hemophilia A or B with known severe or moderately severe factor IX deficiency (≤2% of normal circulating factor IX) by factor activity and/or genetic mutation
4. >150 previous exposure days of treatment with factor VIII or IX protein
5. Have demonstrated capability to independently and accurately understand the risks and benefits of gene therapy and complete informed consent of an approved medical procedure. Have completed an approved gene therapy screening procedure and has the endorsement of their local HTC team

Exclusion

1. History of factor VIII or IX inhibitors
2. Positive factor VIII or IX inhibitor test at pre-gene therapy screening
34. Known history of allergy to corticosteroids
35. Known uncontrolled allergic conditions or allergy/hypersensitivity to any component of the IMP excipients
36. Known medical condition that would require chronic administration of steroids
37. Previous gene therapy treatment or immunity to gene therapy vector (BioMarin absolute, uniQure depending in titer)
38. Receipt of an experimental agent within 60 days prior to screening
39. Current participation or anticipated participation within one year after gene therapy administration in any other interventional clinical trial involving drugs or devices.
CU HTC assessment of “eligible” patients

**Severe Hemophilia A/B patients**

**CU HTC patient population**

<table>
<thead>
<tr>
<th>Subset</th>
<th>Severe случаи</th>
<th>Total случаи</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVIII Severe/total</td>
<td>188</td>
<td>453</td>
</tr>
<tr>
<td>FIX Severe/total</td>
<td>42</td>
<td>146</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>230</strong></td>
<td><strong>599</strong></td>
</tr>
</tbody>
</table>

**US patient population from CDC**

<table>
<thead>
<tr>
<th>Subset</th>
<th>Severe случаи</th>
<th>Total случаи</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVIII Severe/total</td>
<td>9348</td>
<td>21844</td>
</tr>
<tr>
<td>FIX Severe/total</td>
<td>1715</td>
<td>7036</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>11063</strong></td>
<td><strong>28880</strong></td>
</tr>
</tbody>
</table>

**CU HTC Severe Hemophilia A/B > 18 years**

**Hemophilia A (FVIII def.- total = 135)**

- Minus those with current or hx of inh (26) = 109
- Minus HIV (13) = 96
- Minus Hep B (7) = 89
- Minus Hep C (untreated) (3) = 86
- **FVIII total potentially eligible for GT = 86**

**Hemophilia B (FIX def.- total = 29)**

- Minus those with current or hx of inh (0) = 29
- Minus HIV (1) = 28
- Minus Hep B (6) = 22
- Minus Hep C (untreated) (1) = 21
- **FIX total potentially eligible for GT = 21**
Understanding financial implications assuming FDA approval

Recent CO Medicaid rule change negatively effects HTC pharmacy reimbursement
  • Realizing alternative revenue through pharmacy, marketing

Collaboration with the Hemophilia Alliance, regional HTCs, and pharmaceutical sponsors
  • Steve Powell, Treasurer, Board of Directors, Hemophelia Alliance

Present our work in May 2022 and gather CUAMC feedback and evaluation of resources and other programs/collaborations to move forward with CUAMC recognition and support
Pharmacy Implications for becoming a Gene Therapy Infusion Site

Build-out of Clean Room Suite to accommodate sterile compounding ($45,000)

- Negative Pressure Clean Room (ISO 7) with BSC (BioSafety Cabinet) – vented to the outside
- Positive Pressure Ante Room (ISO 7)
- Freezer to accommodate low temperature storage of the Gene Therapy product
- Sterile Compounding PPE and equipment needed for compounding

Policies and Procedures

- Sterile Compounding policies and procedures to include handling of hazardous products
- Training of staff members to perform sterile compounding
- Policies and Procedures for compounding Gene Therapy product, and delivery to the Infusion suite in the clinic
- Purchase of infusion pumps/sets
- Adverse Reaction protocols (emergency medications and procedures)
- Hazardous waste handling
BioMarin: valoctocogene roxaparvovec

**Preceptorship (Invited/selected to start contracting as a training site)**

- An experienced gene therapy HTC will provide our internal Medical Affairs team a real-world, hands-on walkthrough of the dosing day of a patient with a gene therapy.
- The HTC team would educate Medical Affairs on the day of dosing process, best practices, do’s and don'ts, HTC employees involved, and other relevant information with regards to the dosing of patients with gene therapy.

**Infusion Center Selection (will follow preceptorship)**

- A small number of HTCs will be designated by the manufacturer/pharmaceutical company as a regional/national referral center
- Ongoing discussions on a regional level (Mountain States Regional Hemophilia Center Network) regarding infusion site(s) and patient selection and SOC

CSL Behring: etranacogene dezaparvovec

- now establishing a CDA to discuss what an infusion site for them would look like/need to be
Marketing and reputation of the CU HTC

World Federation of Haemophilia
Thought Leader Film Series

• CU HTC featured at the WFH World Forum, May 8-12, 2022, Montreal, CA
• Film(s) highlight Investigator-Initiated clinical and basic research HTC investigators
• 1-minute and 6-minute films
Milestones Measuring our Progress

1. Adoption of “new” Mission, Vision, and Values
2. Importance & buy-in of GTC project
3. Assessment/census of patient population (local & regional)
4. Understanding financial breakeven assuming FDA approval
   a. *New Colorado Medicaid reimbursement, April 1, 2022*
5. Completion of visionary proposal for internal HTC staff/external stake holders
   a. **Discuss service vision {access, clinical excellence}, finances, leadership commitment**
   b. Create detailed, realistic, mutually acknowledged processes & plans
      i. **Clinical protocols of Inclusion/Exclusion, Patient education manual**, Staff education presentation(s), Clinical Care Guideline, Pharmacy manual, Financial tool(s), **Marketing/Branding**
6. Completion of construction of clinical research/infusion facility
   a. **Architecture plans and contracting completed (completion- November 2022)**
CU HTC Gene Therapy Collaborative

• Leadership and close collaboration across the domains of Administration, Clinical care, Program management, Pharmacy and Finance are necessary for success

• Present our work in May 2022 and gather CUAMC feedback and evaluation of resources and other programs/collaborations to move forward with CUAMC recognition and support

• Thank you to the CCTSI, CU AMC Leadership, Lia Gore, M.D., HTC Staff and Patients, Scott Markowitz, M.D, Susan Johnson, Ph.D., Team Building Ahead, Team Wheatless Warriors