Challenging the Paradigms: Liver Transplantation for Metabolic Disease

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Children’s Hospital of Pittsburgh
Consequences of IEMs

Normal | Intoxication | Deficiency

A \downarrow B \quad A \quad C \quad A \downarrow B \quad A \downarrow (b) \quad C \downarrow (b)

SYMPTOMS
Standard Therapy

- Augment missing enzyme activity
- Gene (cell) therapy
- Enzyme replacement/substitution
- Small molecule chaperonins
- Reduce substrate
- Diet or environmental manipulation
- Pathway inhibition or redirection
- Eliminate toxic compounds
- Carnitine
- Ammonia conjugating agents
Goal of metabolic therapy is simple: avert the consequences of imbalance

Metabolic therapy is complicated

- Unavoidable exposures
- Unintended effects
- Unrecognized risks
Consequences of Imbalance
Unavoidable Exposures
Unintended Effects

...Hello? Gary?
Unrecognized Risks
Other Issues

- Non-liver symptoms
- Threshold effect
- Modifier genes
- Environmental effects
- Non-metabolic disease consequences
- Cure vs. improvement
CHALLENGING THE PARADIGMS: LIVER TRANSPLANTATION FOR METABOLIC DISEASE

WELCOME
Liver transplants for OAs
CHP Liver TX Diagnoses

251 Transplants from 1/2000-1/2011
CHP Metabolic Transplants

Disease Indications (%)

- A1AT, 25.6
- MSUD, 13.3
- Familial Cholestasis, 13
- Tyrosinemia, 7
- CF, 6.7
- Wilson, 9.80
- CNS, 5.3
- GSD, 5.3
- Oxalosis, 3.5
- Other, 5.6

1981-2011, n=285
Transplant Survival

Patient Survival by Decade

Legend
- 2000s (n=100)
- 1990s (n=82)
- 1980s (n=103)

2000s
1990s
1980s

p < .000

0 5 10 15 20 25 30 Years

Percent
10 Year Morbidity

- cGFR < 90
- PTLD
- ↑ BMI
- ↑ choles
- ↑ triglyceride

% of patients
Organ Rejection

KM Probability of rejection in 5 year survivors
TX in Propionic Acidemia (26)

- Indications
  - Neonatal onset
  - Poor chronic metabolic control
- Age at transplant
  - Range 7 months-9 years
  - Median 2 years
- Survival
  - 19 still living (73%)
  - 6 deaths at < 1 year post transplant
  - Follow up 7 month-15 years

Metabolic Control in Survivors

- 2 children further decompensation
- 1 metabolic stroke
- 50-60% reduction in serum metabolites
- Persistence of propionyl-carnitine and methyl-citrate in urine

Clinical Parameters

- Improved growth, better feeding
- Normal diet with variable protein restriction
- Stabilized neurologic status
- 2 cases PTLD/CMV/HSV
- Stable renal status
- Cardiomyopathy reversed (1 case)

6 total; 4 neonatal presentation
Main indication: metabolic instability
All had some neurodevelopmental delay
Median age at transplant 1.5 years (0.8-7 years)
1 retransplant (HAT)
PTLD (1), recurrent HSV (1)
All alive and well after median 7.3 yrs (2.2-15 years)
King’s Concerns

- Use kidney-sparing immune suppression
- Late infectious problems
- Unknowns
  - Need for protein restriction
  - Intellectual/neurologic outcome (improvement)
- Overall, worthwhile undertaking
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Count</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>KT (n=6)</td>
<td></td>
<td>2 died sepsis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 diabetes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 chronic rejection</td>
</tr>
<tr>
<td>LT (n=15)</td>
<td></td>
<td>2 died infection, 1 acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 progressive renal failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 neurological disorder (one late stroke)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 infection - bronchiolitis/CMV/EBV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 acidosis</td>
</tr>
<tr>
<td>CLKT (n=6)</td>
<td></td>
<td>1 infection - CMV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 neurological disorder</td>
</tr>
</tbody>
</table>

Metabolic Control (22 Survivors)

- 3 episodes of crisis with 1 death
- Serum MMA decreased by 90%
- Protein intake 1-2 gm/kg/day

Balancing Options

Medical management
- Natural history - phenotype
- Frequency/severity of decompensations
- Risks of end organ damage
- Quality of life/adherence
- Mortality

Liver transplant
- Local organ availability
- Surgical complications
- Early mortality
- Degree of metabolic correction
- Life long immunosupression
- Adherence
Organ Allocation
PELD Scores

**Table 2**

Pediatric End-Stage Liver Disease (PELD) Scoring System

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Regression Coefficient</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Albumin (Log_e value)</td>
<td>-0.687</td>
<td>0.0111</td>
</tr>
<tr>
<td>Total Bilirubin (Log_e value)</td>
<td>0.480</td>
<td>0.0004</td>
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<tr>
<td>INR (Log_e value)</td>
<td>1.857</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Growth Failure (&lt;- 2SD)</td>
<td>0.667</td>
<td>0.009</td>
</tr>
<tr>
<td>Age (&lt;1 Yr.)*</td>
<td>0.436</td>
<td>0.11</td>
</tr>
</tbody>
</table>

*Scores for candidates listed for liver transplantation before the candidate's first birthday continue to include the value assigned for age (<1 Year) until the candidate reaches the age of 24 months.*

Using these prognostic factors and regression coefficients, UNet℠ shall assign a PELD score for each candidate based on the following calculation:

PELD Score = 0.436 (Age (<1 YR.)) − 0.687 x Log_e (albumin g/dL) + 0.480 x Log_e (total bilirubin mg/dL) + 1.857 x Log_e (INR) +0.667 (Growth failure (<- 2 Std. Deviations present))

March 13, 2012

http://optn.transplant.hrsa.gov/policiesAndBylaws/policies.asp
## PELD Priorities

<table>
<thead>
<tr>
<th>Mortality Risk (%)</th>
<th>MELD/PELD Score</th>
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</thead>
<tbody>
<tr>
<td>10%</td>
<td>22/27</td>
</tr>
<tr>
<td>20%</td>
<td>26/35</td>
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<tr>
<td>30%</td>
<td>29/40</td>
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<tr>
<td>40%</td>
<td>31/43</td>
</tr>
<tr>
<td>50%</td>
<td>33/46</td>
</tr>
<tr>
<td>60%</td>
<td>35/49</td>
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<tr>
<td>70%</td>
<td>37/52</td>
</tr>
<tr>
<td>80%</td>
<td>38/55</td>
</tr>
<tr>
<td>90%</td>
<td>41/58</td>
</tr>
</tbody>
</table>
N-carbamylglutamate Consortium

O’Malley Family Foundation

RAREDISEASES
CLINICAL RESEARCH NETWORK

UCDC

H2N=N

CO

OH

NATIONAL INSTITUTES
OF HEALTH

Ennies Kennedy Shriver
National Institute of Child Health
& Human Development

ORPHAN EUROPE

RECORDATI GROUP
# Project Leadership

<table>
<thead>
<tr>
<th>CNMC</th>
<th>Study Sites</th>
<th>Funding/Support</th>
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</thead>
<tbody>
<tr>
<td>PI Mendel Tuchman</td>
<td>CNMC Nicholas Ah Mew</td>
<td>NIH - Mary Lou Oster-Granite</td>
</tr>
<tr>
<td>co-PI Nicholas Ah Mew</td>
<td>BCH Gerard Berry</td>
<td>O’Malley Family</td>
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<tr>
<td>co-PI Study Coordination Avital Cnaan</td>
<td>CHOP Marc Yudkoff</td>
<td>Orphan Europe Marco Ligouri Celine Plisson</td>
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<tr>
<td>Study Manager Kathleen Gillespie</td>
<td>CWRU Douglas Kerr Shawn Mccandless</td>
<td>UCDC Cindy Lemons</td>
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<tr>
<td>Biostatistics Robert McCarter</td>
<td>TCHC Renata Gallagher</td>
<td>OAA Kathy Stagni</td>
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<tr>
<td>Development, FSS testing Penny Glass</td>
<td>UW Lawrence Merritt</td>
<td>PAF Jill Franks</td>
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<tr>
<td>Pharmacy Henry Choi</td>
<td>UCLA Derek Wong</td>
<td>Medical Monitor Jerry Vockley</td>
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<tr>
<td>Neonatology Louis Scavo</td>
<td></td>
<td>DSMB Edward Connor</td>
</tr>
</tbody>
</table>
Protocols

- Long-term outcome of N-carbamylglutamate treatment in Propionic Acidemia and Methylmalonic Acidemia
- Short-term outcome of N-carbamylglutamate in the treatment of acute hyperammonemonia
Participants and Outcomes

Protocol 1
- Newborns with severe PA or MMA randomized to NCG or PLBO during acute illness with hyperammonemia
- Long-term outcome development (standardized testing at 9, 15, 21, 30 months)
- Short-term outcome at each episode (ammonia, FSS, LOH)
- Safety measures

Protocol 2 – Infants and children with severe PA or MMA or late onset OTC or CPS deficiency newly randomized to NCG or PLBO at each episode
- Short-term outcome at each episode (ammonia, FSS, LOH)
- Safety measures

Protocol 3 – Participants in protocols 1 or 2 when stable
- 3 d study pre- and post-NCG (ureagenesis, ammonia, urea amino acids)
- Correlate with outcomes of protocols 1 and 2
Newborns with severe PA or MMA randomized to NCG or PLBO during acute illness with hyperammonemia

Long-term outcome development (standardized testing at 9, 15, 21, 30 months)

Short-term outcome at each episode (ammonia, FSS, LOH)

Safety measures
Infants and children with severe PA or MMA or late onset OTC or CPS deficiency newly randomized to NCG or PLBO at each episode

Short-term outcome at each episode (ammonia, FSS, LOH)

Safety measures
Participants in protocols 1 or 2 when stable
3 d study pre- and post-NCG
(ureagenesis, ammonia, urea amino acids)
Correlate with outcomes of protocols 1 and 2
Protocol 1

First Episode
- Eligibility
- Enrollment & Randomization

Treatment and Monitoring (for 7 days or until discharge)
- NCG or PLBO
- Verification of PA or MMA
- PA or MMA Dx. MMA Dx.
- Ammonia Amino Acids FSS
- Safety Labs

Follow-up (Age 9, 15, 21, 30 mo.)
- Developmental Testing

Recurrent Episodes ≤ 30 months
Protocol 2

Establish eligibility (> 4 weeks of age)

Enrollment

Randomization, Treatment and Monitoring (Duration 7 days or until discharge)

Episode Randomization NCG or PLBO

Ammonia Amino Acids FSS Safety Labs

Recurrent Episodes
Evidence Based Medicine

DOZENS MISSING!
SHOCKING EYEWITNESS REPORTS

ARE UFOs ABDUCTING COWS?

BEFORE

AFTER
A Different View
Childhood Cancer Survival

- Nearly uniformly fatal in 1960
- Current overall 5 year survival rate 75%
- Some cancers with nearly 100% cure rate
Why should You Participate In a Clinical Trial?

- Clinical trials provide the ONLY mechanism for obtaining FDA approval for new treatments.
- There are few FDA-approved treatments for any biochemical disorders.
Children’s Oncology Group

OUR MISSION

To cure and prevent childhood and adolescent cancer through scientific discovery and compassionate care.
All individuals with biochemical disease should have access to standard of care
All should be enrolled in a clinical study to compare standard of care with one other variable
Constant feedback to coordinating centers to incorporate successful changes and discard unsuccessful
“It won’t hurt and it might help.”
“I don’t want (my child) to be a guinea pig.”
“I want (my child) to get the real treatment, not the placebo.”
NO patients = NO trials = NO proven treatments
Teamwork

No man will make a great leader who wants to do it all himself or get all the credit for doing it.

Andrew Carnegie
Thank You!