ALCOHOLIC HEPATITIS: NEW POTENTIAL THERAPIES

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University of Minnesota
Disclosures

• Consultant: Zymogenetics, Vital Therapies, HepaHope, WL Gore and GE
• Grant Support: Ikaria, Novartis, Essai and Bristol Myers Squibb
• I will be discussing the use of ELAD that is non-FDA approved
Case

- A 40-year-old man presents with jaundice
- He has been a heavy alcohol drinker during and since college, ~ 1 quart of spirits per day
- No significant PMH
- No family history of liver disease
- He was self-employed but recently lost his business; he also recently divorced
- No known risk factors for HCV
The patient had stopped drinking 7 days prior to presentation because he was ill.

- AST 166; ALT 35; alkaline phosphatase 188
- Total bilirubin 27.7 mg/dL; INR 3.1
- Serum albumin 2.7 g/dL
- Serum creatinine 0.8 mg/dL
Alcoholic Hepatitis: Diagnosis

- Panlobular inflammation; generally PMNs
- Fatty change is common
- Mallory-Denk bodies
- Chicken wire fibrosis
Assessing Prognosis in Patients With Severe Alcoholic Hepatitis

- Maddrey discriminant function score
  - Discriminant Function = 4.6 * (Pt's PT - Control PT) + Tbili
- MELD
Maddrey Discriminant Function

n = 91 pts, Maddrey < 32
n = 96 pts, Maddrey ≥ 32

P Mathurin, C Mendenhall, R Carithers et al., J Hepatol 2002
MELD

Dunn W et al., Hepatology 2005
Alcoholic Hepatitis: Treatment

- Corticosteroids
- Pentoxifylline
- Nutrition
Corticosteroids Improve Survival of Patients With Severe Alcoholic Hepatitis

Individual Data Analysis of the Last 5 RCTS (Mendenhall, Carithers, Ramond, Cabre*, Philipps*) 221 allocated to Corticosteroids and 197 to controlled groups

![Graph showing survival rates for patients treated with and without corticosteroids](image)

- Patients treated in the corticosteroid group (n=221): 79.97±2.8% survival rate
- Patients treated in the non-corticosteroid group (n=197): 65.7±3.4% survival rate

Significance: p=0.0005

P Mathurin, J O’Grady, RL Carithers Jr, Philipps et al. Gut 2010
Case: Treatment Results

- Screening of infection was negative
- 3 days after admission:
  - Ascites increases
  - MELD score = 30.4
  - Maddrey score = 128
- Prednisolone 40 mg/day was started with a planned duration of 28 days

Results of 1 Week on Corticosteroids

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>27.7 mg/dl</td>
<td>39.1 mg/dl</td>
</tr>
<tr>
<td>INR</td>
<td>3.1</td>
<td>2.5</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.8 mg/dl</td>
<td>0.9 mg/dl</td>
</tr>
<tr>
<td>Albumin</td>
<td>2.7 g/dl</td>
<td>3.5 g/dl</td>
</tr>
</tbody>
</table>
Lille Model (age, change in bilirubin, Scr > 1.3, INR, albumin)

Lille model (N = 350 )

Sensitivity: 83%
Specificity: 84%
Positive predictive value: 83%
Negative predictive value: 84%
Area under the curve: 0.88

P < 0.000001

Louvet A et al, AASLD 2004
Response to Therapy

Distribution Lille score in 3 percentiles: ≤ 35th, 35-70th, ≥70th

- Complete responders [Lille score ≤ 0.16]
  - 91.1 ± 2.7%
- Partial responders [Lille score 0.16-0.56]
  - 79.4 ± 3.8%
- Null responders [Lille score ≥ 0.56]
  - 53.3 ± 5.1%

P < 0.00001

Early Identification of Nonresponders to Corticosteroids at 7 Days

Lille model < 0.45
85±2.5%
P < 0.00001

Lille model ≥ 0.45
25±3.8%

Survival probability

Time (days)

Louvet A et al, Hepatology 2007
Survival Benefit Only in Complete or Partial Responders

**Complete responders**
- Survival: 96\(\pm\)2.2%
- Days: 0, 7, 14, 21, 28
- \(P = 0.005\)

**Partial responders**
- Survival: 80.6\(\pm\)6.6%
- Days: 0, 7, 14, 21, 28
- \(P = 0.03\)

**Null responders**
- Survival: 56.5\(\pm\)7.3%
- Days: 0, 7, 14, 21, 28
- \(P = 0.46\)


Survival benefit is observed only in complete or partial responders.
Pentoxyfilline

Akriviadis Gastroenterology 2000
Treatment of Patients With Severe Alcoholic Hepatitis

- Corticosteroids or pentoxifylline improve short-term survival of patients with severe alcoholic hepatitis
- Nonresponders may be identified early
- Currently, there is no alternative therapy to corticosteroids for nonresponders
WHAT NOW FOR OUR PATIENT?
WHAT NOW FOR OUR PATIENT?

Palliative Care?
Alcoholic Hepatitis: New Potential Treatments

- Liver transplantation
- Liver support devices
Early Liver Transplantation: The French and Belgium Experience

Philippe Mathurin¹, Christophe Moreno², Didier Samuel³, Jérôme Dumortier⁴, Julia Salleron⁵, François Durand⁶, Hélène Castel¹, Alain Duhamel⁵, Georges-Philippe Pageaux⁷, Vincent Leroy⁸, Sébastien Dharancy¹, Alexandre Louvet¹, Emmanuel Boleslawski¹, Valerio Lucidi², Thierry Gustot², Claire Francoz⁶, Christian Letoublon⁸, Denis Castaing³, Jacques Belghiti⁶, Vincent Donckier², François-René Pruvot¹, Jean-Charles Duclos-Vallée³

Brussels, Grenoble, Lille, Lyon, Montpellier, Beaujon, Villejuif

Aims of the Study

1. To determine whether early liver transplantation in nonresponders to medical therapy improves 6-month survival

2. To evaluate alcohol relapse

Early LT in Alcoholic Hepatitis

Methods

• Early liver transplantation in nonresponders undergoing their first event of liver disease

• Nonresponders were identified using Lille score $\geq 0.45$ or worsening of liver function by day 7

• Patient selection was limited to those fulfilling these criteria:
  - Absolute consensus of paramedical and medical staff
  - No co-morbidities
  - Social integration
  - Supportive family members
  - Underwent psychiatric evaluation/addictive profiling
Early LT in Alcoholic Hepatitis

Selection process = 4 team circles

- Nurses, i.e., one resident and one fellow
- Specialist in addiction
- Senior anesthetist and surgeons
- Senior hepatologists

Patient → Time toward complete consensus → Family structure
## Early LT in Alcoholic Hepatitis

<table>
<thead>
<tr>
<th>Transplanted nonresponders</th>
<th>N = 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender no. [%]</td>
<td>15 [57.7%]</td>
</tr>
<tr>
<td>Age (years) median [95%CI]</td>
<td>47.4 [42.7-52.4]</td>
</tr>
<tr>
<td>Duration of corticosteroid treatment (days) Median [95%CI]</td>
<td>11.5 [7-18]</td>
</tr>
<tr>
<td>Hepatorenal syndrome, no. [%]</td>
<td>15 [57.7%]</td>
</tr>
<tr>
<td>Hemodiafiltration or MARS® system no. [%]</td>
<td>10 [38.5 %]</td>
</tr>
<tr>
<td>Infection before transplantation no. [%]</td>
<td>18 [69.2%]</td>
</tr>
<tr>
<td>Mechanical ventilation no. [%]</td>
<td>4 [15.4%]</td>
</tr>
</tbody>
</table>
Early LT in Alcoholic Hepatitis

<table>
<thead>
<tr>
<th></th>
<th>Median [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lille score</td>
<td>0.88 [0.76 – 0.95]</td>
</tr>
<tr>
<td>MELD on first day of therapy</td>
<td>30.1 [27.7 - 33.4]</td>
</tr>
<tr>
<td>MELD day 7</td>
<td>28.5 [26.2 – 33.7]</td>
</tr>
<tr>
<td>MELD at listing</td>
<td>34.2 [29 – 37]</td>
</tr>
<tr>
<td>MELD day 0 - MELD Listing</td>
<td>-5.44 [-7.3 – 2]</td>
</tr>
<tr>
<td>MELD day 7 - MELD Listing</td>
<td>-1.9[-6 – 0]</td>
</tr>
<tr>
<td>Time (days) from end of therapy to listing</td>
<td>13 [6 – 17]</td>
</tr>
<tr>
<td>Time (days) from listing to LT</td>
<td>8.5 [3 – 11]</td>
</tr>
</tbody>
</table>

* Maximum of Lille score is 1
# Early LT in Alcoholic Hepatitis

## Case Control Study

<table>
<thead>
<tr>
<th></th>
<th>Transplanted NRs</th>
<th>Nontransplanted NRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>57.7%</td>
<td>57.7%</td>
</tr>
<tr>
<td>Age</td>
<td>47.4 [42.6 – 52.4]</td>
<td>50.6 [46.5 – 52.6]</td>
</tr>
<tr>
<td>Maddrey score</td>
<td>76.04 [61.2 – 91]</td>
<td>80.6 [66.4 – 97.5]</td>
</tr>
<tr>
<td>Lille score</td>
<td>0.88 [0.76 – 0.95]</td>
<td>0.827 [0.69 – 0.874]</td>
</tr>
</tbody>
</table>
Figure 1: Survival of transplanted patients and their matched non-transplanted controls at 6 months (primary end-point) with extended follow-up at 2 years.

No. at risk
Transplanted 26 20 15 14 13
Matched controls 26 6 6 5 4

Survival (%)

Months

76.9 ± 8.3%
71.4 ± 9.3%
23.1 ± 8.3%

p < 0.001*

* at 6 months (primary end-point)
** at 24 months (extended follow-up)
Early Transplantation Survival Shift of Nonresponders to Responders

• Final combined database included a total of 651 patients; matching was performed using the global optimal algorithm

• For matching criteria, we used the following pre-established ranges: age (+/- 10 years), gender, Maddrey function (< 60; 60-90; and > 90) and Lille score (+/-0.15)

• The overall optimal algorithm was able to select 3 unresponsive matched controls for 20 transplanted patients, 2 unresponsive matched controls for 3 transplanted patients, and only 1 unresponsive matched control for 3 transplanted patients

• The overall optimal algorithm was able to select 4 responsive matched controls for 21 transplanted patients, 2 responsive matched controls for 3 transplanted patients, and only 1 responsive matched control for 2 transplanted patients
Figure 2: Probability of 6-month survival of transplanted patients and their controls randomly selected

<table>
<thead>
<tr>
<th></th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
<th>Month 4</th>
<th>Month 5</th>
<th>Month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplanted</td>
<td>26</td>
<td>21</td>
<td>21</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Random responders controls</td>
<td>92</td>
<td>77</td>
<td>75</td>
<td>71</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>Random unresponsive controls</td>
<td>69</td>
<td>21</td>
<td>21</td>
<td>19</td>
<td>19</td>
<td>19</td>
</tr>
</tbody>
</table>

Survival (%): 85 ± 3.8% for transplanted, 76.9 ± 8.3% for random responders controls, 29.9 ± 5.7% for random unresponsive controls.
Early LT in Alcoholic Hepatitis

- 2 centers have prospective databases of severe alcoholic hepatitis
  - 14 out of 18 transplanted patients were referred by community hospitals
  - Only 4 patients (1.83%) were directly selected by the 2 centers from their own recruitment

- Proportions of early LT among the total number of procedures, and number of procedures for alcoholic liver disease, were 26/891 [2.92%] and 26/315, [8.25%], respectively
Last Analysis of the Patients Transplanted for Severe Alcoholic Hepatitis

• No alcohol relapse within the 6-month period

• 3 patients resumed alcohol consumption during data collection
  - At 720, 740, and 1140 days
  - Despite counseling from addiction specialist, 2 patients remained daily consumers (30 g/day and > 50 g/day, respectively), whereas 1 had occasional consumption (approximately 10 g/week)
Conclusions

• After a first episode of alcoholic hepatitis, early liver transplantation may be proposed in nonresponders as most deaths occur within 2 months during the watch-and-wait period

• Even though early liver transplantation challenges the 6-month abstinence rule, the present results support future evaluation in carefully selected nonresponders
Conclusions

• These encouraging results must be confirmed by other groups

• International database collection of survival and addiction rates is warranted in order to provide more facts and less conjecture in future discussions of the role of early LT in treatment of severe alcoholic hepatitis

• For this objective, the French Minister of Research has decided to devote a grant to development of a database on early LT in alcoholic hepatitis
Unsettled Issues

• In an era of organ shortage, use of liver transplants in severe AH may negatively affect the public attitude towards transplantation and organ donation

• This may cause reluctance on the part of clinicians to modify guidelines for alcoholic patients

• However, patients with “self-inflicted” disease warrant the same access to medical resources as other similar patients
Alcoholic Hepatitis: New Potential Treatments

- Liver transplantation
- Liver support devices
ELAD®: Bioartificial Liver Support System

- Allogeneic cellular therapy
  - 440g of immortalized human C3A liver cells
  - Localized in 4 hollow fiber bioreactors
- Continuous treatment of plasma ultrafiltrate for up to 5 days
- Extra-corporeal support of liver function
ELAD®: Bioartificial Liver
ELAD: Mechanism of Action

• Patient plasma diffuses across 32,000 hollow fiber membranes to interact, then returns to patient
  – Simulates normal liver function

• Interaction performs liver biochemistry and augments liver function
  – Biochemistry. Not filtration or dialysis
  – Processing metabolites and synthesizing necessary proteins

• Proven biochemistries include:
  – Reduction of bilirubin and increase in serum sodium (both proven to affect survival)
  – Production of liver proteins e.g. albumin, transferrin, factor V
  – Operation of P-450 enzyme system

• Short term biomarker response suggests restoration of normal liver function

• Long term survival shows liver recovery
VTI-206  us/eu Phase 2b study aah / non-aah acute on chronic liver failure
VTI-206: Design

- Phase 2b trial in US/EU
- Open-label, randomized, controlled
  - 1:1 randomization to ELAD therapy + standard medical therapy (ELAD) - vs - standard medical therapy alone (control)
VTI-206: Key Entry Criteria

• **Inclusion**
  • 18-67 years old with acute decompensation of chronic liver disease over prior 28 days
  • MELD score 18-35
  • AOCH diagnosis: acute alcoholic hepatitis (AAH) or non-AAH

• **Exclusion**
  • Platelets <50,000/mm³, INR >3.5
  • Chronic renal failure
  • Septic shock, major hemorrhage, spontaneous bacterial peritonitis with uncontrolled systemic infection, hemodynamic instability
  • Significant concomitant disease
  • Previous liver transplant
  • DNR
VTI 206: Non-AAH Cohort (n=25)

- Primary Diagnosis
  - Chronic Alcoholic Liver Disease (n=12)
  - HCV (n=7)
  - Cryptogenic (n=3)
  - HAV/HBV (n=1)
  - NASH (n=1)
  - Autoimmune cholangitis (n=1)
VTI-206: Efficacy Evaluation

- Overall survival (OS) at 30 and 90 days
- Pre-defined analysis populations
  - All subjects, AAH, non-AAH. AAH / non-AAH populations were randomized independently. Results presented by subpopulation.
  - Modified intent-to-treat (MITT) = subjects who received treatment (baseline failures excluded) with 90-day data
  - Per-protocol (PP) = subjects who received ≥72 hrs treatment (ELAD or control)
- OS assessed using Kaplan-Meier survival analysis with 2-tail alpha for log-rank test set at 0.05
## VTI-206: Study Population

<table>
<thead>
<tr>
<th></th>
<th>AAH</th>
<th>Non-AAH</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ELAD</td>
<td>Control</td>
<td>ELAD</td>
</tr>
<tr>
<td>Randomized</td>
<td>16</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td>Baseline failure</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Withdrew consent /</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MITT</td>
<td>15</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>&lt;72 hrs therapy</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>PP</td>
<td>13</td>
<td>16</td>
<td>6</td>
</tr>
</tbody>
</table>

### Reasons for Baseline Failures:

<table>
<thead>
<tr>
<th></th>
<th>AAH</th>
<th>Non-AAH</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Transplant</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Ineligible</td>
<td>0</td>
<td>2* **</td>
<td>2**</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

* DNR, portal vein thrombosis
** Hemodynamic instability, systemic fungal infection
## VTI-206 Demographics - MITT

<table>
<thead>
<tr>
<th></th>
<th>AAH</th>
<th>Non-AAH</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ELAD n = 15</td>
<td>Control n = 16</td>
<td>ELAD n = 9</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 (67%)</td>
<td>8 (50%)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 (60%)</td>
<td>15 (94%)</td>
<td>8 (89%)</td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 (13%)</td>
<td>0</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Age, Mean ± SD</td>
<td>46.4 ± 9.2</td>
<td>49.8 ± 10.3</td>
<td>55.6 ± 8.9</td>
</tr>
<tr>
<td>Baseline MELD,</td>
<td>28.4 ± 5.4</td>
<td>29.3 ± 5.0</td>
<td>27.1 ± 5.8</td>
</tr>
</tbody>
</table>

Mean duration of ELAD treatment (N = 24): 93 hours (range 24 – 144)
VTI-206 Efficacy: AAH Cohort, per-protocol (n=29)

Median survival:
- Control: 65 days
- ELAD: >100 days

No ELAD pt died after 12 days

p = 0.27
HR = 1.9
VTI 206 Efficacy: AAH Cohort

<table>
<thead>
<tr>
<th></th>
<th>MITT</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ELAD n = 15</td>
<td>Control n = 16</td>
</tr>
<tr>
<td>OS through Day 90</td>
<td>9 (60%)</td>
<td>7 (43.8%)</td>
</tr>
<tr>
<td>Median survival, days</td>
<td>&gt;100</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>ELAD n = 13</td>
<td>Control n = 16</td>
</tr>
<tr>
<td>OS through Day 90</td>
<td>9 (69.2%)</td>
<td>7 (43.8%)</td>
</tr>
<tr>
<td>Median survival, days</td>
<td>&gt;100</td>
<td>65</td>
</tr>
</tbody>
</table>

- Differences in survival were not statistically significant (p>0.05) but mathematically favored ELAD
- 1/13 (8%) ELAD-treated and 0/16 Control patients had transplant at 90 days
VTI-206 Efficacy:
Non-AAH Cohort, per-protocol (n=16)

Median survival:
Control: >100 days
ELAD: 33 days

p = 0.12
HR = 2.7
VTI-206 Efficacy: Non-AAH Cohort

<table>
<thead>
<tr>
<th></th>
<th>MITT</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ELAD n = 9</td>
<td>Control n = 11</td>
</tr>
<tr>
<td>OS through Day 90</td>
<td>2 (22.2%)</td>
<td>6 (54.5%)</td>
</tr>
<tr>
<td></td>
<td>ELAD n = 6</td>
<td>Control n = 10</td>
</tr>
<tr>
<td></td>
<td>1 (17%)</td>
<td>6 (60%)</td>
</tr>
</tbody>
</table>

- Differences in survival were not statistically significant (p>0.05)
- 1/6 (17%) ELAD-treated and 4/10 (40%) Control patients had transplant by 90 days
VTI-206: Safety Evaluations

• **Serious adverse events**
  - 28 SAEs reported in 17 ELAD subjects
  - 40 SAEs reported in 20 Control subjects
  - 6 SAEs in 4 ELAD patients reported as possibly related to ELAD: hematemesis, worsening renal failure, vaginal bleeding, sepsis, GI bleeding, intra-vascular hemolysis
Change In Serum Bilirubin (mg/dl)
AAH Cohort, Per-protocol (n=29)

*p<0.05 vs. baseline
Change In Serum T-bilirubin (mg/dl)
Non-AAH Cohort, Per-protocol (n=16)

*p<0.05 vs. baseline
VTI-206: Conclusions

- No unexpected safety issues
- Possible benefit of ELAD for AAH subjects – may provide bridge to recovery and/or transplantation
- No benefit observed in AOCH subjects with acute liver failure due to non-AAH disease
- Pivotal trials planned for 2012 in AAH and fulminant hepatic failure
Development Plan: Primary Indication
Acute Alcoholic Hepatitis

• **Two trials (US/EU)**
  – Primary trial AAH-1 – 200 subjects, up to 46 sites, US/EU
  – Back up trial AAH-2 – 100 subjects, up to 30 sites, EU only, steroid treatment failures

• **Primary trial design (similar to Phase 2b) reviewed by FDA/EMA**
  – Written guidance incorporated into trial design
  – Inclusion criteria tightened based on Phase 2b data
  – Plan revised to reduce potential bias (open-label design)
  – Filed to IND – no safety issues; allowed to enroll by FDA Feb 23
  – IRB filings underway at first 7 sites
  – Conservative statistical plan based on Phase 2b outcome: 90% power to detect difference in median survival of ~50 days (125 vs 75 days) with 152 subjects
  – Allows for DSMB-mediated futility analysis at 75 enrolled

• **Back up trial design under review by EMA for allowance by June 2012**
  – >75% mortality in steroid failures defined by “Lille” criteria (validated method)
  – Design proposed by EMA
Development Plan: Secondary Indication Fulminant Hepatic Failure

- Single trial (US/EU): 75 subjects at same primary sites
- Enroll only subjects listed for transplant: plan slower enrollment
- End points:
  - Primary: 30-day overall survival
  - Secondary: Bridge-to-transplant or recovery
- Inclusion criteria similar to first pilot trial
- Data available same time as the back up AAH study
- Use as back-up study or for label expansion
Alcoholic Hepatitis: Factoids

- Minimum alcohol use to put one at risk is 80 gm/day for males.
- Of males who consume 80 gms of alcohol per day, 2% will develop ALD.
- **WOMEN ARE 4X MORE SUSCEPTIBLE TO ALD**