INAUGURAL LIVER CONNECT

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The Puzzle in Hepatorenal Syndrome Management

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Disclosures

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• Editorial Board Involvement: American Journal of Gastroenterology
Thomas D. Boyer
1943-2018
Objectives

• At the end of the presentation, the attendee will:

  – Have a clear understanding of the modern definition of Acute Kidney Injury in setting of liver disease.
  – Define the ideal strategies to manage this clinical problem using vasoconstrictors.
  – Have an understanding of the impact of AKI-HRS in the setting of liver transplantation and MELD.
  – Have a strategy to prevent and manage AKI-HRS.
• Serum creatinine of 1.5 g/dL corresponds to GFR of ~30 mL/min in cirrhosis

• Due to low muscle mass in cirrhosis, SCr overestimates renal function

Prevalence of Different Types of AKI in Hospitalized Patients With Cirrhosis

Hospitalized Patients With Cirrhosis

- Chronic kidney disease 1%
- Acute kidney injury 19%

Prerenal 68%

Intrarenal (eg, ATN) 32%

Postrenal <1%

Volume responsive 66%
  (hypovolemia, infection, vasodilators)

Not volume responsive

- HRS type 1, 25%
- HRS type 2, 9%

Pathophysiology of AKI-HRS

Renal Failure in Cirrhosis

Probability of Survival

Days

0.0 0.2 0.4 0.6 0.8 1.0

0 30 60 90

- Parenchymal nephropathy
- Hypovolemia
- Infection
- HRS

Defining AKI in Cirrhosis

Traditional criteria (ICA)\(^{[a]}\)
- 50% increase in SCr over baseline
- Cutoff value of SCr: 1.5 mg/dL

New definition\(^{[b]}\)
- ↑ in SCr ≥ 0.3 mg/dL within 48 hours
- or ↑ SCr ≥ 50% from baseline that is known or presumed to have occurred within the prior 7 days

References:
Stages of AKI in Patients With Cirrhosis

Stage 1
• Increase in SCr ≥0.3 mg/dL or an increase in SCr ≥1.5-fold to 2 fold from baseline
• 1A vs 1B is based on absolute SCr level of 1.5 mg/dL

Stage 2
• Increase in SCr >2 to 3-fold from baseline

Stage 3
• Increase of SCr >3-fold from baseline or SCr ≥4.0 mg/dL with an acute increase ≥0.3 mg/dL or initiation of RRT

Progressive Impact on Survival in Cirrhosis and AKI

Kidney Disease and Waitlist Mortality

74,771 listed from July 1st, 2007 to July 1st, 2014

52,091 excluded
- 25,372 exception points
- 20,293 <90 days listed
- 2114 FHF
- 2929 age <18
- 1337 LDLT
- 46 error in listing

22,680 included patients in analysis

Increase in sCR ≥0.3 mg/dL in last 7d OR <72d of HD?

AKI

AKI on CKD

Both

eGFR <60 mL/min for 90d AND current eGFR of ≤30 mL/min OR ≥72d of HD?

CKD

Neither

Normal

Kidney Disease and Waitlist Mortality

Outcome After Liver Transplant

- Among patients with AKI-HRS receiving transplant, non-responders required RRT more frequently than responders (20% vs 0%; \(P = .024\))

- Non-responders to HRS treatment had a significantly higher incidence of CKD at 1 year after LT than responders (65% vs 31%; \(P = .019\))

- Non-response to terlipressin and albumin was found to be an independent predictor for CKD at 1 year after LT (SHR = 2.76; \(P = .001\))

- Responders to terlipressin and albumin did not have an increased risk (SHR = 1.53; \(P = .210\))

AKI in Cirrhosis
When Is It HRS?

- Diagnosis of cirrhosis and ascites
- Diagnosis of AKI (as per the AKIN criteria)
- No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin (1 g/kg of body weight, 100 g max)
- Absence of shock
- No current or recent use of nephrotoxic drugs
- No macroscopic signs of structural kidney injury defined as:
  - Absence of proteinuria (>500 mg/d)
  - Absence of microhematuria (>50 RBCs/hpf)
  - Normal findings on renal ultrasonography

Management
AKI-HRS Treatment Desired Outcomes

• Less RRT
  – Improve RRT-free survival
• Facilitate medical management
• Potential to return to compensated state
• Shorter ICU stays
• Liver transplant patients
  – Less RRT
  – Improved survival
Management Based on ICA-AKI Stage

Initial AKI* stage 1a*

- Close monitoring
  - Remove risk factors (withdrawal of nephrotoxic drugs, vasodilators and NSAIDs, taper/withdraw diuretics and β-blockers, expand plasma volume, treat infections* when diagnosed)

- Resolution
- Persistence
- Progression

Initial AKI* stage >1a*

- Withdrawal of diuretics (if not yet applied) and volume expansion with albumin (1 g/kg) for 2 days

Response?

- YES
  - Does AKI meet criteria of HRS?
    - NO
      - Specific treatment for other AKI phenotypes
    - YES
      - Vasoconstrictors and albumin

- NO
  - Further treatment of AKI decided on a case-by-case basis

*AKI at the first fulfilling of KDIGO criteria

Pharmacologic Therapy for HRS

IV Albumin
- 0.5 to 1 g/kg (max 100 g/d) for resuscitation
- Then 25 to 50 g/d

Vasoconstrictors
- Midodrine (± octreotide)
- Norepinephrine
- Terlipressin
Albumin
Role in the Treatment of Cirrhosis and Its Complications

**Albumin functions**

- **Oncotic pressure**
  - Negative charge
  - High concentration
  - Intravascular distribution

- **Capillary permeability**
  - Hemostatic effect
  - Extracellular distribution
  - Cys-34
  - High concentration

- **Solubilization, transport, metabolism**
  - Antioxidant
  - Endotoxin binding inactivation
  - Intracellular glutathione
  - TNF-induced NF-κB activation
  - Intracellular distribution

- **Immunomodulation**
  - Endotoxin binding inactivation
  - Intracellular glutathione
  - TNF-induced NF-κB activation
  - Intracellular distribution

- **Endothelial stabilization**
  - Negative charge
  - Electrostatic binding
  - Specific binding sites
  - Cys-34

- **Antioxidant**
  - Cys-34
  - N terminal: Metal binding
  - Bilirubin binding

How Do We Define Response to Treatment?

- In cases of recurrence of HRS-AKI upon treatment cessation, repeat course of therapy

Complete response

Final SCr within 0.3 mg/dL of the baseline value

Partial response

Regression of AKI stage to a final SCr ≥0.3 mg/dL above baseline value

EASL. J Hepatol. 2018.
## Comparison of Vasoconstrictors in HRS Treatment

<table>
<thead>
<tr>
<th></th>
<th>Short-Term Mortality</th>
<th>Reversal of HRS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>Quality of Evidence</td>
</tr>
<tr>
<td><strong>Efficacy vs placebo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midodrine + octreotide</td>
<td>0.61 (0.19, 1.93)</td>
<td>Low (network)</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>0.75 (0.32, 1.76)</td>
<td>Low (network)</td>
</tr>
<tr>
<td>Terlipressin</td>
<td>0.65 (0.41, 1.05)</td>
<td>Moderate (direct; imprecision, low event rate)</td>
</tr>
<tr>
<td>Dopamine + furosemide</td>
<td>0.70 (0.12, 4.13)</td>
<td>Low (network)</td>
</tr>
<tr>
<td><strong>Efficacy vs midodrine + octreotide</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>1.50 (0.60, 3.78)</td>
<td>Low (network)</td>
</tr>
<tr>
<td>Terlipressin</td>
<td>1.14 (0.39, 3.33)</td>
<td>Very low (network)</td>
</tr>
<tr>
<td>Dopamine + furosemide</td>
<td>1.14 (0.15, 8.76)</td>
<td>Very low (network)</td>
</tr>
<tr>
<td><strong>Efficacy vs noradrenaline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terlipressin</td>
<td>0.93 (0.43, 1.98)</td>
<td>Low (network)</td>
</tr>
<tr>
<td>Dopamine + furosemide</td>
<td>0.93 (0.14, 6.17)</td>
<td>Low (network)</td>
</tr>
<tr>
<td><strong>Efficacy vs terlipressin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine + furosemide</td>
<td>1.00 (0.18, 5.67)</td>
<td>Low (network)</td>
</tr>
</tbody>
</table>

Vasoconstrictors Available in US vs Terlipressin

Cavallin et al. (2015)
- Terlipressin (N=27)
- Midodrine and Octreotide (N=21)

HRS Reversal (%)

- 55.5%
- 4.8%

Arora et al. (2020)
- Terlipressin (N=24)
- Norepinephrine (N=10)

HRS Reversal (%)

- 40.0%
- 16.7%

Terlipressin
Terlipressin: Not Yet Available in US

- **Synthetic vasopressin analogue**
  - Prodrug for LVP; 1% of its V₁ activity
  - LVP slowly released via tissue peptidase metabolism

- **Slow release is advantage over vasopressin**
  - $T\frac{1}{2} \approx 50$ min (LVP $T\frac{1}{2} \approx 3$ h)
  - Reduces portal inflow and portal pressure

- **Administered IV**
  - Typical treatment period is 6 days (up to 14 d)
Terlipressin Phase 3 Program

- **OT-0401 Study**
  - N=112
  - Supportive

- **REVERSE Study**
  - N=196
  - Additional Data

- **CONFIRM Study**
  - N=300
  - Pivotal

Timeline:
- 2004 | 2005 | 2006
- 2010 | 2011 | 2012 | 2013
- 2016 | 2017 | 2018 | 2019
CONFIRM Study Design

Pre-Study Period

Albumin Fluid Challenge ≥2 Days

R 2:1

Active Study Period

Terlipressin (N = 199)

Placebo (N = 101)

Day 4 Dose Decision

Day ≤14

Follow-Up Period

Day 30

Day 60

Day 90

### Demographics and Baseline Characteristics

**CONFIRM Study**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Terlipressin N = 199</th>
<th>Placebo N = 101</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>54.0 (11.3)</td>
<td>53.6 (11.8)</td>
</tr>
<tr>
<td>Sex, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>60.3</td>
<td>58.4</td>
</tr>
<tr>
<td>Alcoholic hepatitis present, %</td>
<td>40.7</td>
<td>38.6</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3.5 (1.0)</td>
<td>3.5 (1.1)</td>
</tr>
<tr>
<td>Minimum, maximum</td>
<td>2.3, 6.9</td>
<td>2.1, 6.2</td>
</tr>
<tr>
<td>SIRS, %</td>
<td>42.2</td>
<td>47.5</td>
</tr>
<tr>
<td>MELD score, mean (SD)</td>
<td>32.7 (6.6)*</td>
<td>33.1 (6.2)†</td>
</tr>
<tr>
<td>Baseline ACLF grade 3, %</td>
<td>20.1</td>
<td>17.8</td>
</tr>
<tr>
<td>Bilirubin, mean (SD), mg/dL</td>
<td>13.0 (13.4)‡</td>
<td>15.2 (15.8)§</td>
</tr>
<tr>
<td>CLIF-SOFA score, mean (SD)</td>
<td>10.4 (2.4)‖</td>
<td>10.8 (2.5)¶</td>
</tr>
</tbody>
</table>

## Components of Primary Endpoints
### CONFIRM Study

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Two consecutive serum creatinine values of ≤ 1.5 mg/dL collected at least 2 hours apart</td>
</tr>
<tr>
<td>2</td>
<td>No incidence of RRT within 10 days after second confirmatory serum creatinine</td>
</tr>
<tr>
<td>3</td>
<td>Must be alive for at least 10 days after second confirmatory serum creatinine</td>
</tr>
</tbody>
</table>

Primary Endpoint: Verified HRS Reversal
CONFIRM Study

## Secondary Endpoint Results

### CONFIRM Study (ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>Terlipressin n = 199 %</th>
<th>Placebo N = 101 %</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRS reversal (SCr ≤1.5 mg/dL)</td>
<td>36.2</td>
<td>16.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Durability of HRS reversal (No RRT for 30 days)</td>
<td>31.7</td>
<td>15.8</td>
<td>.003</td>
</tr>
<tr>
<td>HRS reversal in the SIRS subgroup</td>
<td>33.3</td>
<td>6.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Verified HRS reversal with no recurrence of HRS by day 30</td>
<td>24.1</td>
<td>15.8</td>
<td>.092</td>
</tr>
</tbody>
</table>

Incidence of RRT Post Liver Transplant
CONFIRM Study (ITT Population)

- **Terlipressin (N=46)**: 19.6%
  - **n = 9**

- **Placebo (N=29)**: 44.8%
  - **n = 13**

\[ P = .036 \]
HRS Reversal by Subgroups
Pooled ITT Population

<table>
<thead>
<tr>
<th>Baseline SCr, mg/dL</th>
<th>Odds Ratio (95% CI)</th>
<th>Terlipressin % (n/N)</th>
<th>Placebo % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3.0</td>
<td></td>
<td>49.2 (62/126)</td>
<td>29.8 (25/84)</td>
</tr>
<tr>
<td>≥3.0 and &lt;5.0</td>
<td></td>
<td>28.0 (51/182)</td>
<td>11.5 (16/139)</td>
</tr>
<tr>
<td>≥5.0</td>
<td></td>
<td>9.1 (4/44)</td>
<td>3.0 (1/33)</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
<td>Present</td>
<td>38.0 (46/121)</td>
<td>13.1 (11/84)</td>
</tr>
<tr>
<td>SIRS subgroup*</td>
<td>Present</td>
<td>7.7 (6/78)</td>
<td>35.7 (40/112)</td>
</tr>
<tr>
<td>Baseline MAP, mm Hg</td>
<td>&lt;70</td>
<td>33.0 (29/88)</td>
<td>14.3 (10/70)</td>
</tr>
</tbody>
</table>

*SIRS status only collected in CONFIRM and REVERSE studies.
FDA Briefing Document. NDA 22231 Terlipressin.
# Most Common Adverse Events (≥10%)  
Integrated Studies (Safety Population)

<table>
<thead>
<tr>
<th>Preferred Term* ‡</th>
<th>Terlipressin N = 349 %</th>
<th>Placebo N = 249 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>21.5</td>
<td>12.4</td>
</tr>
<tr>
<td>Nausea</td>
<td>15.2</td>
<td>12.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14.9</td>
<td>5.6</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>11.7</td>
<td>7.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10.3</td>
<td>6.4</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>8.6</td>
<td>11.2</td>
</tr>
</tbody>
</table>

*Up to 7 days after the end of treatment; ‡Patients with multiple AEs of 1 preferred term are counted once.

FDA Briefing Document. NDA 22231 Terlipressin.
### Most Common Serious Adverse Events (≥5%)

**Integrated Studies (Safety Population)**

<table>
<thead>
<tr>
<th>Preferred Term*†</th>
<th>Terlipressin N = 349 %</th>
<th>Placebo N = 249 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total with any SAEs</td>
<td>65.0</td>
<td>59.8</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>8.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Multiple organ dysfunction syndrome</td>
<td>7.4</td>
<td>3.2</td>
</tr>
<tr>
<td>Chronic hepatic failure</td>
<td>6.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>6.0</td>
<td>9.2</td>
</tr>
<tr>
<td>Sepsis</td>
<td>5.2</td>
<td>1.6</td>
</tr>
</tbody>
</table>

*Up to 30 days posttreatment; †Patients with multiple AEs of 1 preferred term are counted once.

FDA Briefing Document. NDA 22231 Terlipressin.
Clinical Perspective on Risk Management

• Optimize benefit/risk for each patient
• Avoid treating those with most advanced disease
  – SCr ≥5 mg/dL or ACLF Grade 3
• Respiratory failure mitigation
  – Protect airway
  – Treat hepatic encephalopathy
  – More nuanced management of fluid balance
  – More aggressive management of respiratory issues
  – Stop or avoid terlipressin in florid pulmonary edema or pneumonia
How Do We Work These Strategies
Prevention of HRS

• Albumin administration following large volume paracentesis reduces the risk of post paracentesis circulatory dysfunction and improves survival\textsuperscript{[a]}

• Primary prophylaxis against SBP in at risk patients reduces the risk of HRS and mortality\textsuperscript{[b]}

• Albumin administration in patients with SBP reduces the risk of HRS from 30.6% to 8.3% \( (P = .01) \textsuperscript{[c]} \)

• Long-term use of weekly albumin in patients with decompensated cirrhosis and ascites may reduce incidence of HRS (OR 0.39, CI: 0.19, 0.76)\textsuperscript{[d]}

Conclusions

- HRS is a common complication of decompensated cirrhosis
- Associated with high mortality in critically ill population
- Vasoconstrictor therapy is the mainstay of treatment
- Liver transplant is the definitive therapy
- Reversal of HRS pre-transplant is associated with improved outcomes