Hepatitis C in the Liver Transplant Recipient: Progress and Problems

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NIH Hepatitis C Research Center
National Jewish Integrated Program in Immunology
• I have nothing to disclose

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HCV Center Grant and VA Merit Review
Spectrum of Disease

Acute HCV Infection

15%-30%
Recovery

70%-85%
Chronic HCV Infection

Chronic Hepatitis C

Mild
Moderate
Severe

Cirrhosis

End-Stage Liver Disease

Liver Transplantation

Hepatocellular Carcinoma

Death

25 years

Adapted from Hoofnagle JH. Hepatology. 1997;26(suppl 1):16S.
Case: Severe Hepatitis C after Liver Transplantation

- Mr T.R. is a 47 yo man s/p liver transplantation for hepatitis C-related liver failure at UCLA

- Within 3 years, he developed evidence of allograft cirrhosis and underwent re-transplantation

- 6 months after re-transplantation, he is jaundiced (T. bili 20 mg/dL) and has ascites
Case Questions/Overview

• Hyper-accelerated natural history of HCV
  - What are causative factors of allograft cirrhosis?
  - Can they be modified or used for targeted therapy?
• Is it appropriate to offer re-transplantation?
Magnitude of the problem

- HCV-related liver disease is the single leading indication for liver transplantation worldwide
- HCV-positive OLT recipients have an increased rate of death and allograft failure
- HCV RNA recurrence is universal
- At 5 years, >20-40% of HCV-positive OLT recipients have evidence of allograft cirrhosis
  - May be higher after 5 years
Early Viral Kinetics After Liver Transplantation: Reinfection is Universal

Garcia-Retortillo; Hepatology 35: 680-687
Histologic Findings: HCV positive vs. negative liver transplant recipients

Gane, NEJM 1996
HCV is a different model after transplantation

Pre-Transplant

Post-Transplant

Courtesy of Jay Burton
Survival in Pre- and Post-OLT HCV Cirrhosis

Patient Survival

<table>
<thead>
<tr>
<th>Months</th>
<th>0%</th>
<th>20%</th>
<th>40%</th>
<th>60%</th>
<th>80%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>100%</strong></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td></td>
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</tbody>
</table>

Pre-OLT STAGE Post-OLT

- No cirrhosis
- Compensated
- Decompensated

Berenguer, 2000; Prieto, 2000; Fattovitch, 1997
Back to Case 1: OKT3 use associated with greater risk of allograft cirrhosis

Case control analysis:
- 19 HCV+ patients who received OKT3 and 33 age, gender, initial immunosuppression matched controls (steroid responsive rejection)

  26% of patients who received OKT3 for steroid-resistant rejection developed allograft cirrhosis (vs. 6% in control group).

- 50% of patients who develop allograft failure due to recurrent HCV had received OKT3;
  - Relative Risk 9.77 (3.57-28.8).
  - *Transplantation* 1997; 63: 17

- Does OKT3 increase risk of severe HCV or are patients more likely to receive OKT3 because of atypical HCV recurrence?
Factors Associated with Graft Loss Due to HCV Recurrence

234 grafts (209 patients) - 74 failures → 29 due to HCV recurrence (12.3%)

<table>
<thead>
<tr>
<th></th>
<th>#</th>
<th>RR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeated pulses of steroids</td>
<td>19</td>
<td>3.2 (1.7-16.0)</td>
<td>0.013</td>
</tr>
<tr>
<td>OKT3 use</td>
<td>15</td>
<td>2.8 (1.0-14.0)</td>
<td>0.036</td>
</tr>
</tbody>
</table>

OKT3 (anti-CD3 monoclonal antibody) for steroid-resistant rejection
Recovery from acute HCV is associated with vigorous CD4+ T cell responses

Missale et al., JCI 1996

P < .0001
Recovery from acute HCV is marked by vigorous, sustained CD4+ responses.
HCV-specific CD4+ T cell Responses Correlate with Severity of HCV Recurrence

* $p = .03$

35/35 14/35 8/8 0/8

% patients with immune response

Gastroenterology 1999; 117: 926-932
Early HCV-specific CD4+ T cells correlate with mild recurrence
Protein Position Sequence
Core 131-140 ADLMGYIPLV
NS3 1073-1081 CINGVCWTV
NS3 1406-1415 KLVALGINAVV
NS5 2594-260 ALYDVVTKL

**CD8+ T cell analysis: Tetramers**

1. Peptide binds to MHC class I (α1-α2)
2. β2m binds to MHC class I (α3)
3. Biotin binds to streptavidin
4. Tetramer formation
5. Phycoerythrin (PE) fluorochrome

**Flow Cytometry**

- T-cell receptors
- CD8
- Tetramer + PE
- anti-CD8-FITC
- Flow cytometer

**Graph**

- Fluorescence: PE (tetramer)
- Fluorescence: FITC (CD8)
- CD8+ tetramer+ green
- CD8+ tetramer- red
- CD8- tetramer- blue
- CD8- tetramer+ pink

**Legend**

- CD8+ human T cell
- Tetramer + PE
- anti-CD8-FITC
- Flow cytometer
Reconstitution of Immune Responses after Tx of Cholestatic HCV Recurrence (HLA A2+/A2+)

Weston, Hepatology 2005
Abrogation of Immune Responses in HCV Recurrence Unresponsive to Rx (HLA A2+/A2+)

Patient 12

- Viral Load
- T-Bilirubin
- Core
- E2
- NS3
- NS4
- NS5

Start of IFN/Ribavirin Therapy

Months Post-Transplant

Prototype 1a sequence (CINGVCWTV)

- V----
- V----
- V----
- V-----
Factors Associated with more Severe HCV Recurrence

- **Pre-transplant**
  - High viral load
  - HIV co-infection
  - Retransplant for recurrent HCV
  - Donor Age > 50
  - Genetic Polymorphisms (cytokines) in Donor or Recipient?

- **Post-transplant**
  - High viral load (4 months)
  - Steroids for acute rejection
  - OKT3 use
  - CMV infection
  - Impaired HCV-specific Immunity
Cumulative probability of developing HCV related graft fibrosis (S≥4, Ishak): effect of donor age (Berenguer 2002)
Influence of *IL28B* Genotypes in PEG-IFN/RBV Treatment

C allele associated with higher SVR

N=1137 (from IDEAL trial)
Differential Effects of IL-28B (IFNL3) on HCV recurrence

Risk of severe recurrent HCV after liver transplant in 225 recipients, by donor and recipient *IL28B* rs12979860 genotype presented as non-CC (TT or CT) compared to CC genotype in donors (D) and recipient (R). The [C] allele thought to be favorable in the non-transplant setting, is associated with increased risk of severe recurrent HCV when present in the donor liver graft. *Reference is the lowest risk combination of donor non-CC and recipient CC genotype. n, number in each group.

Biggins, J Hepatology 2013
Back to the Case: Recurrent HCV Infection, When to Treat?

Cirrhosis  OLT  Normal histology

Pre-OLT 0 4-6 weeks 6 months Years

Pre-emptive Acute hepatitis Chronic hepatitis

Established recurrence
Challenges with Treating Recurrent HCV in LT Recipients

- High HCV RNA levels
- High prevalence of genotype 1
- Previous non-responders
- Insulin resistance
- Poor clinical status and tolerability
- Immunosuppression
- Cytopenias
- Renal insufficiency

Surprising antiviral therapy works at all!

Negative predictors for virological response in non-LT patients

Additional limitations in LT recipients
Who should be treated?

Stage of Fibrosis

Antiviral therapy

Imperative

“Wait and see”

No need

Annual protocol liver biopsies

Stage ≥2 fibrosis

Antiviral therapy

Villamil, 2006

OLT 1 2 3 4 5 Years

0 1 2 3 4
Treatment of Established Recurrence

All Reported Trials: SVR

<table>
<thead>
<tr>
<th></th>
<th>IFN</th>
<th>PEG</th>
<th>IFN-RIB</th>
<th>IFN-RIB → RIB</th>
<th>PEG-RIB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0/12</td>
<td>12/33</td>
<td>5/165</td>
<td>14/87</td>
<td>155/496</td>
</tr>
<tr>
<td></td>
<td>4%</td>
<td>33%</td>
<td>21%</td>
<td>16%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Arial, APT 2008
PEG-IFN/Riba improves survival

- 165 patients with HCV recurrence
  - 78 patients treated
  - Similar MELDs and fibrosis @ recurrence
- Cox regression analysis showed Tx associated with decreased overall graft failure (HR 0.34)

Veldt, AJT 2008
De Novo Autoimmune Hepatitis (AIH) with allograft dysfunction following PEG/Rib Treatment

- during or shortly after treatment, 9 of 54 (17%) developed LFTs, histologic evidence of AIH (8 of 9 were HCV RNA negative)
  - Antivirals stopped, steroids started
  - 4 developed progressive liver failure, HCV RNA neg

• >30% infiltrate composed of plasma cells; absent endothelialitis, eos, immature lymphoid cells

Back to the Case...Retransplantation (ReTx) for HCV

• Worldwide experience in ReTx for HCV recurrence
  - Natural history post-ReTx

• Optimizing utility in the current MELD allocation schema

• Current practice patterns in the U.S.
  - Factors used to select ReTx candidates
Allocation of a Scarce Resource: Basic Principles

Justice
Duty to distribute resources equitably

Stewardship
Conflict

Utility
Duty to promote best outcome in the aggregate
Allocation of a Scarce Resource: Basic Principles

Duty to promote individual patient’s best interest

Justice
Duty to distribute resources equitably

Stewardship Conflict

Utility
Duty to promote best outcome in the aggregate
Evolution of Anti-HCV Therapy

Response rates (%)

Timeline

IFN 3X week
1989

IFN 3X week and Ribavirin
1998

Pegylated IFN and Ribavirin
2001

Pegylated IFN, Ribavirin, and NS3 Protease Inhibitor
2009-2011
### Treatment of Chronic HCV: Sustained Virologic Response (SVR) With Peginterferon and Ribavirin

<table>
<thead>
<tr>
<th></th>
<th>Peg-IFN $\alpha$-2a$^{1,2}$</th>
<th>Peg-IFN $\alpha$-2b$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>56% &amp; 63%</td>
<td>54% (61%)*</td>
</tr>
<tr>
<td>Genotype 1</td>
<td>46% &amp; 52%</td>
<td>42% (48%)*</td>
</tr>
<tr>
<td>Genotype 1, HVL</td>
<td>41% &amp; 46%</td>
<td>30% (37%)*</td>
</tr>
<tr>
<td>Genotypes 2 &amp; 3</td>
<td>76% &amp; 84%</td>
<td>82% (88%)*</td>
</tr>
</tbody>
</table>

*RBV >10.6 mg/kg by post hoc analysis.
SVR = sustained virologic response; HVL = high viral load.
Telaprevir (Incivek)

Boceprevir (Victrelis)

NS3/4A Protease Inhibitors (approved May 2011)
Rosen HR, NEJM 2011; 364: 2429-2438
Drug-Drug Interactions

• Both boceprevir and telaprevir are inhibitors of CYP3A

• Many common medications are metabolized by this enzyme, and boceprevir and telaprevir may affect their plasma concentrations

• Interactions with CsA and Prograf are very important

# Boceprevir and Telaprevir Contraindications

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Contraindicated Drugs</th>
<th>Boceprevir</th>
<th>Telaprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG CoA Reductase Inhibitors</td>
<td>Lovastatin, simvastatin (pravastatin okay because not P450 dependent)</td>
<td>✔️</td>
<td>✓ (also atorvastatin)</td>
</tr>
<tr>
<td>Oral Contraceptives</td>
<td>Drosperinone</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>PDE5 Enzyme Inhibitor</td>
<td>Sildenafil or tadalafil when used for the treatment of pulmonary arterial hypertension</td>
<td>✔️</td>
<td>✓</td>
</tr>
<tr>
<td>Neuroleptic</td>
<td>Pimozide</td>
<td>✔️</td>
<td>✓</td>
</tr>
<tr>
<td>Sedative/Hypnotics</td>
<td>Triazolam; orally administered midazolam</td>
<td>✔️</td>
<td>✓</td>
</tr>
</tbody>
</table>

# Boceprevir and Telaprevir Contraindications

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<th>Telaprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha 1-Adrenoreceptor antagonist</td>
<td>Alfuzosin</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine, phenobarbital, phenytoin</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Antimycobacterial</td>
<td>Rifampin</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ergot Derivatives</td>
<td>Dihydroergotamine, ergonovine, ergotamine, methylergonovine</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>GI Motility Agent</td>
<td>Cisapride</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Herbal Products</td>
<td>St. John's Wort (Hypericum perforatum)</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Triple Therapy Post-LT: The University of Colorado Experience

James R. Burton, Jr., MD
Associate Professor of Medicine
Medical Director of Liver Transplantation
University of Colorado Hospital
## Increase in Single-dose CSA, TAC AUC Due to Multi-dose Boceprevir or Telaprevir
(n Healthy Volunteers without Chronic Hepatitis C)

<table>
<thead>
<tr>
<th></th>
<th>CSA</th>
<th>TAC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir</td>
<td>2.70</td>
<td>17.1</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>4.64</td>
<td>70.3</td>
</tr>
</tbody>
</table>


* Sirolimus and Everolimus are expected to behave similarly to tacrolimus. No data.
Telaprevir use in Liver Recipient

Switch to CSA+MMF*
Monitor for 4 weeks

LADR to achieve MTD of P/R

\(\frac{1}{4}\) CSA dose QOD* MMF*
TPV-TT for 12 Weeks

eRVR
HCV RNA neg wk 4 & 12

Additional 24 weeks of P+R

Adjust CSA dose and Monitor for Rejection

Check HCV RNA at MTD for measure of IFN sensitivity

Monthly HCV RNA to check VR and for resistance

After TPV is stopped, daily CSA levels, upward adjust CSA dose/freq

NO eRVR “Slow Responder”

Additional 36 weeks of P+R

All treatment is discontinued if HCV RNA is >1000 IU/mL at week 4 or 12 or detectable at week 24 of Triple Therapy

* TPV increases CSA exposure by 5-fold – for CSA total daily dose 200 mg decreased to 50 mg QOD.
* MMF added to reduce risk of rejection if converting from TAC to CSA and when CSA dose reduced
Overall Virological Response

N=18

HCV RNA (IU/ml)

Weeks of Antiviral Therapy Since Start of TT

18-43
Time to HCV RNA Negativity After Starting TT

HCV RNA positive 24 weeks after starting TT

Median: 15 days
Range: 7-110 days

Days from start of TT to HCV RNA <18 IU/ml

On TT at last f/u

Patient

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

110
55
49
# Summary of Virologic Response

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVR (HCV RNA negative at 4 weeks)</td>
<td>12/18</td>
<td>67%</td>
</tr>
<tr>
<td>eRVR (HCV RNA negative at 4 and 12 weeks)</td>
<td>8/15(^1)</td>
<td>53%</td>
</tr>
<tr>
<td>HCV RNA negative at 24 weeks</td>
<td>6/12(^2)</td>
<td>50%</td>
</tr>
<tr>
<td>Viral breakthrough:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presumed viral resistance to telaprevir</td>
<td>2/18</td>
<td>11%</td>
</tr>
<tr>
<td>Breakthrough after TT</td>
<td>3/15(^1)</td>
<td>20%</td>
</tr>
</tbody>
</table>

\(^1\) Three patients have not completed 12 weeks of TT

\(^2\) Twelve patients have completed 24 weeks of antiviral therapy
CRUSH-C study (5 centers)
Anemia is significant problem
  78% dose reduction of ribavirin
  79% prescribed erythropoietin
  48% needed blood transfusions
  7% hospitalized for anemia

### Blood Transfusion Requirement

<table>
<thead>
<tr>
<th></th>
<th>Before TT</th>
<th>During TT</th>
<th>After TT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td># patients*</td>
<td>1</td>
<td>8</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td># transfusion episodes</td>
<td>1</td>
<td>22</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td># units of PRBCs</td>
<td>2</td>
<td>48</td>
<td>10</td>
<td>60</td>
</tr>
</tbody>
</table>

*3 patients had transfusions at more than one interval
**Summary: HCV and OLT**

- HCV is the single leading indication for OLT and is associated with diminished patient and graft survival.

- Approximately 20%-30% HCV+ OLT recipients will develop evidence of allograft cirrhosis by year 5.

- Factors associated with more aggressive HCV recurrence include multiple/severe rejection, older donor age, impaired HCV-specific immunity.
Summary: HCV and OLT

• Antiviral therapy is effective in only a subset of patients and is associated with significant side effects.
  - Efficacy of Direct-Acting Antivirals in this setting promising but complicated
    • eRVR > 50%
  - Need to better identify non-responders to avoid unnecessary toxicities

- Careful with Alloimmune/Autoimmune Hepatitis after viral eradication
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Social Workers

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Questions?