Guilty as Charged!

Hepatitis C and Liver Transplantation

Norah Terrault, MD, MPH
Professor of Medicine
Director, Viral Hepatitis Center
University of California, San Francisco

- HCV ± HCC accounts for ~40% of LT in the U.S.
- Plateau in waitlist registration since 2000
  - Related to improved outcomes in cirrhotics
- Increase of HCC among wait-listed patients
  - Preferential assignment in organ allocation priority
  - Related to epidemiology of HCV in the U.S. population
- Post-transplant survival of HCV-infected patients is inferior to non-HCV-infected patients

Waitlist Registrants with HCV United States


Predicted Future Prevalence of HCV in the United States

Armstrong et al, Hepatology, 2000;31:777-782
HCV Post-Transplant Patient Survival

- HCV+ recipients have 30% higher mortality c/w non-HCV+ recipients after 5 yrs follow-up

Recurrent HCV Disease

“The Facts”

- ~10% develop severe, early recurrence with graft loss within 2-5 years of LT
- 20-30% develop recurrent cirrhosis within 5 years
  - High risk groups known: AA, HIV+, older donors
- Median time to cirrhosis = 8-10 years
  - Time to reach cirrhosis decreasing over time
    - Donor factors likely of primary importance
- Retransplantation for recurrent disease is controversial
  - Not a realistic option for most patients

Optimizing Outcomes in Transplant Recipients with HCV

- Minimize factors contributing to progressive disease
  - Donor selection
  - Post-transplant management of risk factors
- Treatment strategies to prevent or treat recurrent HCV disease
  - Viral suppression or eradication
  - Slow down progression to cirrhosis

Forman, Gastroenterology 2002
Factors Associated with Fibrosis Progression

- **Recipient Factors**
  - AA race
  - HIV coinfection
  - Female gender

- **Donor Factors**
  - Older donor age
  - Prolonged cold ischemia time
  - Higher donor risk index

- **Viral Factors**
  - Higher HCV RNA at time of transplant
  - HCV genotype 1 (controversial)

- **Transplant-related Factors**
  - Treated acute rejection
  - CMV infection
  - Post-transplant diabetes

- **Immunosuppression?**

Donor Age and Rate of Graft Loss in HCV-Infected Patients

- Lake J, Am J Transplant 2005

Extended Criteria Donors and HCV Risk of Graft Loss

- Maluf DG, Liver Transplant 2009

A2ALL Study Cohort

- Graft Survival
  - DDLT vs LDLT>20 vs LDLT≤20

- Terrault N et al. Liver Transplant 2007

Comparison | P value  
--- | ---  
DDLT vs. LDLT>20 | 0.572  
DDLT vs. LDLT≤20 | <0.001  
LDLT>20 vs. LDLT≤20 | 0.002
LDLT versus DDLT Fibrosis Progression

Factors predictive of advanced fibrosis:
- 0.19 U/yr DDLT
- 0.11 U/yr LDLD

Factors predictive of advanced fibrosis:
- Older donor age
- DDLT
- CIT

Multivariate:
- Donor age >45 yr RR=8.17


HCV and Donor Decisions

Effect on Fibrosis Progression

- Older donors are RISKY
  - Donors over 50 yrs associated with significant >2-fold higher risk of cirrhosis within 5 years
  - Older donors with prolonged CIT or other adverse donor factors are TOO HIGH RISK

- Living donors do not have increased risk of worse outcomes with HCV
  - May provide advantage as younger donors and short CIT but more studies needed

Modifying Other Risk Factors for Fibrosis Progression

<table>
<thead>
<tr>
<th>Factor</th>
<th>Potential Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIT</td>
<td>Keep CIT short (&lt;8 hours)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Less diabetogenic IMS Weight optimization</td>
</tr>
<tr>
<td>Treated acute rejection</td>
<td>Don’t treatment mild rejection Avoid steroid boluses &amp; lymphocyte-depleting drugs Sufficient IMS to prevent acute rejection</td>
</tr>
<tr>
<td>CMV infection</td>
<td>Prophylaxis to prevent infection</td>
</tr>
</tbody>
</table>

Optimizing Outcomes in Transplant Recipients with HCV

- Minimize factors contributing to progressive disease
  - Donor and peri & post-transplant factors

- Treatment strategies to prevent or treat recurrent HCV disease
  - Viral suppression or eradication
  - Slow down progression to cirrhosis
Management of Recurrent HCV

- Prevent graft infection
- Reduce risk of disease progression
- Prevent cirrhosis and graft failure
- Primary treatment strategy

Pre-Transplant Antiviral Therapy

Preemptive Antiviral Therapy

Antiviral therapy for recurrent disease

Listed

Management of Recurrent HCV

Pre-transplant eradication reduces the risk of hepatitis C after liver transplantation. Reduction in viral load prior to LT may reduce time to or severity of recurrent HCV. Viral eradication in decompensated cirrhotic may delay time to transplantation or death.

Risks:
- Risk of worsening decompensation
- Hypersplenism --> cytopenias potentially dose-limiting
- Increased incidence of bacterial infections

Pre-Transplant Antiviral Therapy to Prevent HCV Recurrence

- Randomized controlled trial
  - LDLT recipients or DDLT recipients with MELD upgrade for HCC
  - All genotype 2/3 treated; genotype 1 randomized 2:1 to treatment
  - Treatment-naive (39%) or treatment-experienced (61%) with inadequate prior course of Peg-IFN + RBV

- Exclusion Criteria
  - MELD >20, Creatinine > 2.2 mg/dL
  - Hemoglobin < 10 g/dL, ANC < 750, Platelet count < 35K

Everson GT et al. Hepatology 2009;50(4):302A

Low Ascending Dose Regimen (LADR)

PEG-2b

Initial Dose: 0.75 mcg/kg/wk

Week 1:
- Full Dose 1.5 mcg/kg/wk
  - If ANC > 750 & PIt > 35K

Week 2:
- Further Dose Adjustments as Required

Week 3:
- Full Dose 1200 mg/d
  - Target 10.6-13.2 mg/kg/d

RBV

Initial Dose: 600 mg/d

Week 1:
- 800 mg/d
  - If Hgb > 10

Week 2:
- 1000 mg/d
  - Target 10.6-13.2 mg/kg/d

GCSF, EPO or both, used prior to and during treatment

Antiviral Therapy in Cirrhotics on the Waiting List

- Rationale:
  - Pre-transplant eradication reduces the risk of hepatitis C after liver transplantation
  - Reduction in viral load prior to LT may reduce time to or severity of recurrent HCV
  - Viral eradication in decompensated cirrhotic may delay time to transplantation or death

- Risks:
  - Risk of worsening decompensation
  - Hypersplenism --> cytopenias potentially dose-limiting
  - Increased incidence of bacterial infections

1Forns, J Hepatol 2003;39:389-396
2Everson, Hepatology 2005;42:255-262
Post-Transplant Virologic Response (pTVR)

% of treated LT patients

- Overall: 29% (11/40)
- Genotype 1: 19% (4/22)
- Genotype 2/3: 88% (7/18)

P=0.17

1 3 additional treated patients have been transplanted, but 12 wk HCV RNA not available (2 died, 1 result pending). 15 had LDLT and 25 had DDLT.

Efficacy of Pre-Transplant Antiviral Treatment

- Genotype 1
  - ETVR: 30/124
  - Post-LT SVR: 50/124

- Genotype 2/3
  - On-Treatment: 24/30
  - Post-LT SVR: 8/30

Everson, Hepatology 2005;42:255-262
Forns, J Hepatol 2003:39:389-396

Effect of Treatment Duration on % HCV RNA Negative at LT and pTVR

Treatment duration only independent predictor of pTVR, p=0.04

- <10 weeks: 45% (6/13), 13% (2/13)
- 10 to 15 weeks: 44% (7/17), 16% (5/11)
- >15 weeks: 99% (11/11), 88% (7/8)

Adverse Events (AEs), Serious AEs (SAEs), and Deaths

- p<0.0001 (58/59), p=0.04 (44/59)

- % of Patients
  - AEs: 58/59 (10/20), 14/20 (8/20)
  - SAEs: 44/59 (10/20), 10/20 (3/20)

- Deaths: 14% (8/59), 10% (3/20)
### Treatment of Wait-Listed Patients

**Conclusions**
- Efficacy limited by rate of on-treatment responses
  - Only ~20% of treated genotype 1 patients will achieve desired benefit
  - Time to negative and duration of negativity important
- Pre-treatment antiviral therapy comes at a cost!
  - Higher rate of adverse effects than untreated patients
  - Infection risk post-LT needs more study
- Select patients:
  - Not too sick and confident of treatment duration of ≥12 weeks
  - LDLT best, HCC upgrades good

**What to Recommend in 2010?**

Use Very Selectively

- Consider if:
  - HCC and LDLT with compensated cirrhosis and low MELD
  - Favorable genotypes, relapsers, low baseline viral load
  - Confident that at least 12 weeks treatment doable

### Treatment of Recurrent HCV in Transplant Recipients

- Mainstay of management
- Consensus to treat if “significant” or “progressive” histologic disease
- Generally means:
  - Cholestatic hepatitis
  - Presence of fibrosis – usually F2/4 or higher
  - Necroinflammation grade 3 or 4
- Goal of therapy = viral eradication
  - Survival benefit shown

**Challenges of Antiviral Therapy in Transplant Recipients**

**“More Difficult to Eradicate” Population**
- High prevalence of HCV genotype 1
- High pretreatment HCV RNA
- Previous non-response to IFN

**Higher Risk of Complications**
- Risk of precipitating acute or chronic rejection
- Infectious complications
  - Combined effects of IMS and antiviral therapy
- More limited tolerability
  - Cytopenias common
  - Renal dysfunction related to CNIs
Efficacy of Post-Transplantation Peg-IFN and RBV

Results of Metaanalyses

<table>
<thead>
<tr>
<th>Author</th>
<th>Years included</th>
<th>N (per study)</th>
<th>SVR Overall</th>
<th>SVR G1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang</td>
<td>1980-2005</td>
<td>587 (11-86)</td>
<td>27%</td>
<td>--</td>
</tr>
<tr>
<td>Berenguer</td>
<td>2002-2006</td>
<td>611 (12-61)</td>
<td>30%</td>
<td>29%</td>
</tr>
<tr>
<td>Xiouchakis</td>
<td>1999-2008</td>
<td>264* (13-54)</td>
<td>44% (ARR 31%)</td>
<td>32%</td>
</tr>
</tbody>
</table>

*Controlled trials, peginterferon and ribavirin vs low dose or no treatment


Histologic Responses in Virologic Non-Responders

Treatment with Peg-IFN + RBV for ≥48 wks
Biopsy done at 24 weeks post-treatment

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>% Stable or Improved NI</th>
<th>% Stable or Improved Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrion</td>
<td>2007</td>
<td>N=54</td>
<td>--</td>
<td>42%</td>
</tr>
<tr>
<td>Hanouneh</td>
<td>2008</td>
<td>n=15</td>
<td>--</td>
<td>35%</td>
</tr>
<tr>
<td>Berenguer</td>
<td>2006</td>
<td>N=67</td>
<td>74%</td>
<td>61%</td>
</tr>
</tbody>
</table>

61% if biochemical response
30% if no biochemical response

Tolerability and Safety of Peginterferon + Ribavirin

- Dose reductions/discontinuations
  - Peg-IFN: 40-60% reduction → 10-36% stop
  - Ribavirin: 50-90% reduction → 20-50% stop
- Rejection: low but not zero
  - Median acute rejection= 2%
- “Plasma cell hepatitis”, “de novo autoimmune hepatitis”
  - Described at/near time of viral clearance
  - Associated with IMS reductions in some cases
  - Variable prognosis, can progress to graft loss

Kugoh, M Liver Transplant 2003
Fai M, Liver Transplant 2008
Berard G, Sci. 2007

Predictors of Sustained Virologic Response (SVR)

- Baseline characteristics
  - Non-1 genotype
  - Low baseline HCV RNA level
  - Shorter time from transplantation
  - Milder histologic recurrence
  - Cyclosporine-based immunosuppression
- On-Treatment characteristics
  - RVR best predictor of SVR
  - Adherence to drug doses
  - Duration of HCV RNA undetectability

Oton, Am J Transplant, 2006
Naoumov, Am J Transplant, 2006
Castells, J Hepatol, 2005
Hanouneh, Liver Transplant 2008
Carrion, Gastroenterology, 2007
Dosing Peg-IFN and Ribavirin in Transplant Recipients

- Early discontinuation of peg-IFN = no SVR \(^1\,^2\,^3\)
- Dose reductions associated with reduced SVR rates

"Dose to tolerability" is usual approach

Sharma, Liver Transplantation, 2007
Berenguer, Liver Transplantation, 2006
Hanouneh, Liver Transplantation, 2007

CsA-based IMS and SVR Rates

- Predictors of SVR:
  - CsA: OR = 3.11 (95% CI 1.32-7.29)
  - Genotype 2/3: OR = 7.89 (95% CI 2.41-25.4)
  - Younger donor age: OR=0.96 (95% CI 0.93-0.99)
  - Less necroinflammation: OR 0.37 per Metavir grade (95% CI 0.18-0.75)

On-Treatment Predictors of Response

N=53, 79% genotype 1
Peg-IFN (alfa 2a or 2b) + RBV for 48 wks

<table>
<thead>
<tr>
<th></th>
<th>PPV (95% CI)</th>
<th>NPV (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>100% (63-100)</td>
<td>88% (69-98)</td>
</tr>
<tr>
<td>Genotype 1</td>
<td>100% (40-100)</td>
<td>91% (72-99)</td>
</tr>
<tr>
<td>EVR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>63% (44-80)</td>
<td>100% (81-100)</td>
</tr>
<tr>
<td>Genotype 1</td>
<td>48% (30-74)</td>
<td>100% (81-100)</td>
</tr>
</tbody>
</table>

Honouneh, Liver Transplant 14:53-58, 2008

Efficacy of Extended Antiviral Treatment for Slow Responders

- Single center, uncontrolled study, N= 34 patients
  - All genotype 1b and LDLT recipients
- Individualized treatment duration: 12 mos of treatment after disappearance of serum HCV RNA
  - 18/36 became HCV RNA negative within 12 mos of treatment initiation (range, 1.2-9.9; median, 4.0)
  - Total treatment durations =13.2 - 21.9 mos (median 16)
- SVR rates 50% overall but ....
  - Only 6% relapse rate (1/18) who had extended treatment
  - All patients in extended protocol completed study

Ueda Y, Transplantation, 2010
Antiviral Therapy for Recurrent HCV
Current Status

- SVR rates modest but benefits huge
  - SVR in ~30% for genotype 1; >60% for genotype 2/3
  - Stabilization or improved fibrosis in majority, especially in those with SVR
  - Survival advantage only evident in responders

- New themes
  - Treat at earlier stage/grade of disease
  - Adjust treatment duration to virologic responses (RGT)
  - Consider CsA-based IMS

- Tolerability is major limitation – especially RBV
  - Use of growth factors supported by post-hoc analyses (associated with increased SVR rates)
  - Will continue to be limitation, even with direct antivirals

Post-LT Antiviral Treatment Protease Inhibitors – The Next Step

- STAT-C drugs can be expected to increase significantly the proportion of patients achieving on-treatment and sustained virologic responses

The Reality:
- Protease inhibitors applicable only genotype 1
- Don’t work so well in NRs (e.g. Telaprevir ~SVR 40%)
- Tolerability will be challenge
  - Drug interactions (some PIs and CNIs)
  - Anemia (significant with both telaprevir and boceprevir)

Managing Recurrent HCV Disease 2010 and Beyond

- Ability to eradicate HCV remains suboptimal
  - Especially for genotype 1 patients
  - STAT-C drugs will help, especially in pre-LT treatment strategy, but will not be a panacea

- Continued efforts to minimize disease progression (buy time for more drugs to become available)
  - Donor selection probably most critical issue
  - Prevent acute rejection, CMV infection, and diabetes