New Hepatitis C Therapies
Expectations vs Reality

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HCV as Indication for Liver Transplantation

- HCV ± HCC accounts for ~40% of LT in the U.S.
- Plateau in waitlist registration since 2000
  - Related to improved outcomes in cirrhotics
  - Related to epidemiology of HCV in U.S. population
- 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
HCV Post-Transplant Patient Survival

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

Graph showing survival rates over 10 years for different conditions:
- PBC: 6933
- Alcoholic: 6933
- HBV: 2406
- HCV: 5967

ELTR- 01/1988 - 12/2001
Forman, Gastroenterology 2002
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

Relatively limited time for intervention
Treatment Strategies for HCV

- Listed
- Prevent graft reinfection

- Transplant
- Prevent recurrent disease

- Chronic hepatitis
- Prevent progressive disease and graft failure

- Graft loss

- Pre-Transplant Antiviral Therapy

- Preemptive Antiviral Therapy

- Antiviral therapy for recurrent disease
Antiviral Therapy in Cirrhotics on the Waiting List

Rationale:

- Pre-transplant achievement of SVR eliminated the risk of hepatitis C after liver transplantation \(^1,^2\)
- Pre-transplant achievement of an undetectable HCV RNA level while on treatment reduces the likelihood of having recurrent HCV after transplantation
- Viral eradication in cirrhotic may delay time to transplantation or death

\(^1\) Forns, J Hepatol 2003:39:389-396
\(^2\) Everson, Hepatology 2005;42:255-262
Antiviral Therapy in Cirrhotics on the Waiting List

- **Concerns:**
  - Cytopenias, especially anemia
    - Need for growth factors, blood transfusion
  - Increased incidence of bacterial infection
    - During treatment
    - In early post-transplant period
  - Worsening liver disease
    - Magnitude of risk poorly characterized but related to MELD/CPT status at start of treatment
Wait-Listed Patients Treated with Peg-IFN + RBV: Post-Transplant Virologic Response

Forns X, J Hepatol 2003:39:389-396
Effect of Treatment Duration on % HCV RNA Negative at LT and Post-LT

Treatment duration only independent predictor of post-LT viral negativity (pTVR), p=0.04

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

- **AEs**: 98% (58/59) vs. 70% (14/20) in Treated vs. Untreated, \( p < 0.0001 \)
- **SAEs**: 75% (44/59) vs. 50% (10/20) in Treated vs. Untreated, \( p = 0.04 \)
- **Deaths**: 14% (8/59) vs. 15% (3/20) in Treated vs. Untreated, \( p = 0.68 \)

Serious Adverse Events Relative to Time of Liver Transplantation

All SAEs

Overall p=0.04

- Pre-LT: 54% Treated, 20% Untreated
- Post-LT Infections: 44% Treated, 8% Untreated
- Post-LT <30d: 67% Treated, 46% Untreated

Infectious SAEs

Overall p=0.09

- Pre-LT: 17% Treated, 0% Untreated
- Post-LT <30d: 12% Treated, 0% Untreated
- Post-LT >30d: 35% Treated, 23% Untreated

Treated

Untreated
Treatment of Wait-Listed Patients with Peg-IFN and RBV

Conclusions

- Efficacy limited by rate of on-treatment responses
  - Only ~20% of treated genotype 1 patients will achieve desired benefit
  - Duration of HCV RNA negativity is important predictor of success in preventing HCV recurrence post-LT

- Pre-treatment antiviral therapy comes at a cost!
  - Higher rate of adverse effects than untreated patients, especially of infections
  - Infection risk period appears to extend into post-LT phase
Protease Inhibitors

“Great Expectations”
SVR Rates in G1 Treatment-Naive with PI-Combination Therapy

SVR Rates with PI-Combination Therapy in G1 Rx-Experienced

Direct antiviral drugs (e.g. PIs) expected to increase significantly the proportion of patients achieving an on-treatment virologic response.

Advantages

Higher rates of on-treatment virologic responses achievable
Time to HCV RNA negativity shorter → shorter duration therapy needed

Disadvantages

Side effects and risks more not less than with Peg-IFN and RBV
Risk of PI drug resistance may limit post-transplant options
Genotype 1, compensated cirrhosis (Child-Pugh A), previous relapse or partial response to peg-IFN/RBV
- TVR 750 mg TID + peg-IFN alfa-2a 180 µg/wk + RBV 1000-1200 mg/day for 12 wks followed by pegIFN/RBV for 36 wks

% HCV RNA undetectable

- Wk 4: 51 (145/285)
- Wk 8: 79 (224/282)
- Wk 12: 78 (219/281)
- Wk 16: 71 (177/251)

Median duration at treatment: 84 days

CUPIC: Efficacy of Boceprevir in Cirrhotics

- Genotype 1, compensated cirrhosis (Child-Pugh A), previous relapse or partial response to peg-IFN/RBV
- BOC-based therapy: 4-wk peg-IFN alfa-2b 1.5 µg/kg/wk + RBV 800-1400 mg/day lead-in phase followed by BOC 800 mg TID + peg-IFN/RBV for 44 wks

Median duration of treatment: 140 days

## Safety of PI-Triple Therapy in Cirrhotics

<table>
<thead>
<tr>
<th>Safety Outcome, %</th>
<th>Boceprevir-Based Therapy (n = 159)</th>
<th>Telaprevir-Based Therapy (n = 296)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events</td>
<td>38.4</td>
<td>48.6</td>
</tr>
<tr>
<td>Premature treatment discontinuation</td>
<td>23.9</td>
<td>26.0</td>
</tr>
<tr>
<td>▪ Resulting from serious adverse events</td>
<td>7.4</td>
<td>14.5</td>
</tr>
<tr>
<td>Death</td>
<td>1.3 (N=2)</td>
<td>2.0 (N=6)</td>
</tr>
</tbody>
</table>
|                                            | Infection/sepsis [n = 2]          | Infection/sepsis [n = 3],
|                                            |                                   | variceal bleed [n = 1],
|                                            |                                   | encephalopathy [n = 1], and
|                                            |                                   | lung carcinoma [n = 1])          |
| Grade 3/4 non-hematologic adverse events   |                                   |                                   |
| ▪ Infection                                | 2.5                               | 8.8                               |
| ▪ Rash                                     | 0                                 | 7.5                               |
| ▪ Hepatic decompensation                   | 4.4                               | 4.4                               |
### Safety of PI-Triple Therapy in Cirrhotics: Hematologic Adverse Events

<table>
<thead>
<tr>
<th>Safety Outcome, %</th>
<th>Boceprevir-Based Therapy (n = 159)</th>
<th>Telaprevir-Based Therapy (n = 296)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anemia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Grade 2</td>
<td>22.6</td>
<td>19.6</td>
</tr>
<tr>
<td>• Grade 3/4</td>
<td>10.1</td>
<td>10.1</td>
</tr>
<tr>
<td>• Use of erythropoietin</td>
<td>66.0</td>
<td>56.8</td>
</tr>
<tr>
<td>• Blood transfusion</td>
<td>10.7</td>
<td>15.2</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Grade 3/4</td>
<td>6.9</td>
<td>13.1</td>
</tr>
<tr>
<td>• Use of thrombopoietin</td>
<td>1.9</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>Neutropenia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Grade 3/4</td>
<td>5.0</td>
<td>4.7</td>
</tr>
<tr>
<td>• Use of G-CSF</td>
<td>3.8</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Pre-Transplant HCV Treatment
What to Recommend in 2012?

- PI-triple therapy indicated in select patients
  - Child’s A cirrhosis $\rightarrow$ best candidates those with HCC or living donor
  - Risk-benefit most favorable in patients with high likelihood of on-treatment response: relapsers, IL28 genotype CC, low HCV viral load

- Treatment specifics
  - TVR indicated only in CP-A, if early CP-B $\rightarrow$ use BOC
  - Lead-in may be useful with both PIs to establish tolerability and likelihood of response
  - Optimal duration of HCV RNA negativity pre-LT unknown $\rightarrow$ longer duration expected to be better
Pre-Transplant HCV Treatment
What to Recommend in 2012?

- High rate of treatment-associated adverse effects
  - Risk of infections, severe anemia, liver decompensation

- Key aspects of management
  - Seriously consider whether patient likely to tolerate peg-IFN and ribavirin
  - Close monitoring
  - Aggressive management of cytopenias
  - Antibiotic prophylaxis

- Work closely with the transplant team
  - Timing of treatment initiation in relationship to expected LT
  - Rescue of patients who get into trouble
Treatment Strategies for HCV

**Listed**
- Prevent graft reinfection

**Transplant**
- Prevent recurrent disease

**Chronic hepatitis**
- Prevent progressive disease and graft failure

**Graft loss**
- Antiviral therapy for recurrent disease

- Pre-Transplant Antiviral Therapy
- Preemptive Antiviral Therapy
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

Weisner R, Liver Transpl 2003
Picciotto FP, J Hepatol, 2007
## 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>Xirouchakis</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

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
Neumann, Am J Transplant, 2006
Castells, J Hepatol, 2005
Hanouneh, Liver Transplant 2008
Carrion, Gastroenterology 2007
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
Protease Inhibitors

“Great Expectations”
Pi-Triple Therapy in Liver Transplant Recipients

- Addition of PI can be expected to increase the proportion of patients achieving sustained virologic responses
- But.....
  - Protease inhibitors applicable only genotype 1
  - Protease inhibitors work less well in prior partial and null-responders to peg-IFN and RBV
  - Drug interactions (PIs and CNIs/sirolimus)
  - Tolerability will be challenge
    - Anemia (significant with both telaprevir and boceprevir)
Drug-Drug Interactions

- TPV and BOC block CYP 3A4 and P-glycoprotein → CSA, TAC, Sirolimus levels increase

<table>
<thead>
<tr>
<th>Healthy Volunteer Study</th>
<th>Effect on CsA levels</th>
<th>Effect on Tac levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telaprevir</td>
<td>4.6-fold increase</td>
<td>70-fold increase</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>2.7-fold increase</td>
<td>17-fold increase</td>
</tr>
</tbody>
</table>

- DDI studies not done with sirolimus

- Neither cyclosporine nor tacrolimus affected telaprevir or boceprevir levels

*Hulskotte, Hepatology 2012; Garg, Hepatology 2011*
HCV PI Therapy for HCV Recurrence Following Liver Transplantation

- Multicenter experience
  - Chronic GT1 HCV infection
  - HCV recurrence: ≥ F2 (n = 20)
    or cholestatic hepatitis (n = 8)
- Off label use (different regimens):
  - P/R lead-in for 4 wks → BOC 800 mg TID + P/R (n = 17)
  - P/R lead-in for 4 wks,
    followed by TVR 750 mg TID + P/R (n=5)
  - TVR 750 mg TID + P/R (n=6)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BOC + P/R (n = 17)</th>
<th>TVR + P/R (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis stage ≥ F3, %</td>
<td>53</td>
<td>55</td>
</tr>
<tr>
<td>Cholestatic hepatitis, %</td>
<td>24</td>
<td>36</td>
</tr>
<tr>
<td>Cyclosporine, %</td>
<td>65</td>
<td>45</td>
</tr>
<tr>
<td>Tacrolimus, %</td>
<td>35</td>
<td>55</td>
</tr>
<tr>
<td>Mycophenolate mofetil, %</td>
<td>41</td>
<td>27</td>
</tr>
<tr>
<td>HCV RNA, log_{10} IU/mL (range)</td>
<td>7.0 (5.9-8.5)</td>
<td>7.1 (5.2-8.3)</td>
</tr>
<tr>
<td>ALT*, IU/L</td>
<td>191</td>
<td>99</td>
</tr>
<tr>
<td>Total bilirubin, μmol/L</td>
<td>52</td>
<td>47</td>
</tr>
<tr>
<td>CrCl, mL/min</td>
<td>83</td>
<td>73</td>
</tr>
<tr>
<td>Neutrophil count, cells/mm³</td>
<td>2900</td>
<td>2100</td>
</tr>
<tr>
<td>Platelet count, cells/mm³</td>
<td>142,000</td>
<td>145,000</td>
</tr>
</tbody>
</table>

HCV PI Therapy for HCV Recurrence Following Liver Transplantation

- 56-70% of patients achieved HCV RNA undetectability by week 8 of treatment

HCV PI Therapy for HCV Recurrence Following Liver Transplantation

- Calcineurin inhibitor dose reductions required
  - BOC group
    - Cyclosporine dose ↓ 1.3-fold
    - Tacrolimus dose ↓ 5.0-fold
  - TVR group
    - Cyclosporine dose ↓ 4-fold
    - Tacrolimus dose ↓ 35-fold

- Anemia was very frequent AE
  - 71% with BOC; 55% with TVR
  - > 90% of pts required EPO

- 1 death in TVR group

Post-Transplant HCV Treatment
What to Recommend in 2012?

- PI-triple therapy should be used with caution and only in patients with greatest need
  - Higher stages of fibrosis, cholestatic hepatitis
- More drugs -> more side effects
  - Anemia management is a major issue
- Beware of drug-drug interactions
  - Decrease CNI dose when PI added; increase CNI dose when PI interrupted or stopped
- Minimize risk of resistance
  - Insure compliance with protease dosing schedule
  - Adhere to futility rules – stop PI if suboptimal response
Future HCV Therapy

Current Step

- Protease Inhibitors
  + Ribavirin
  + Peg-Interferon

Desired Step

- DAA + DAA and/or RBV
Interferon-Free Therapy for Genotypes 2 and 3

- Treatment-naïve, non-cirrhotic, stratified by HCV genotype and IL28B status
- Randomized 1:1:1:1 to IFN-free or IFN-sparing arms 1-4
  - GS-7977 alone added as exploratory arm

Lawitz E, et al. Hepatology 2011; 54: 472A
Co-Pilot Study
Boosted PI + Non-Nuc + RBV

<table>
<thead>
<tr>
<th>Arm 1</th>
<th>Treatment-naïve (N=19)</th>
<th>ABT-450/r 250/100 mg QD + ABT-333 400 mg BID + RBV*</th>
<th>12 wk f/u</th>
<th>95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 2</td>
<td>Treatment-naïve (N=14)</td>
<td>ABT-450/r 150/100 mg QD + ABT-333 400 mg BID + RBV*</td>
<td>12 wk f/u</td>
<td>93%</td>
</tr>
<tr>
<td>Arm 3</td>
<td>Prior P/R non-responders (N=17)</td>
<td>ABT-450/r 150/100 mg QD + ABT-333 400 mg BID + RBV*</td>
<td>12 wk f/u</td>
<td>47%</td>
</tr>
</tbody>
</table>

†All subjects followed for 48 weeks after end of treatment

*Weight-based ribavirin 1000-1200mg/day

Poordad F, EASL 2012
IFN-free Studies in the Transplant Setting

- Wait-listed patients with HCC, Childs-A cirrhosis, all genotypes
  - GS-7977: 400 mg per day RBV: 1000mg - 1200mg per day (weight based)
- Immediate Post-LT (Preemptive therapy)
  - ITX 5061 ITX 5061 (150mg) pre-transplant, immediately post-transplant and daily thereafter for 1 week
- Post-transplant recurrent disease
  - Coming soon.....

www.clinicaltrials.gov
The Reality: PI Triple Therapy

- **Positives:**
  - Higher on-treatment and SVR rates likely
  - Pre-transplant strategy offers advantage of shorter duration treatment

- **Negatives**
  - Side effects greater
  - Significant drug-drug Interactions → potentially severe consequences
  - Cirrhotics and transplant recipients are relatively interferon-resistant → will still be non-responders
  - Emergence of viral resistance may be more common
  - Use in transplant recipients is off-label

Urgent need for more effective and better tolerated therapies