The Use of Protease Inhibitors for the Treatment of Hepatitis C in Liver Transplant Recipients: Is a Bird in the Hand Worth Two in the Bush?

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Learning Objectives:
1. Describe the impact of hepatitis C on liver transplantation
2. Evaluate the literature regarding the utilization of protease inhibitors in the liver transplant population
3. Propose a strategy for the future treatment of liver transplant recipients with hepatitis C virus genotype 1
HEPATITIS C VIRUS

I. Epidemiology
   A. Global\textsuperscript{1-3}
      i. Approximately 170-200 million people are infected worldwide
      ii. 3 to 4 million new infections occur each year
      iii. Over 350,000 deaths annually
   B. United States\textsuperscript{4,5}
      i. Approximately 4 to 7 million Americans have chronic hepatitis C (HCV) infection
      ii. 17,000 Americans are estimated to become infected with HCV each year
   C. Texas\textsuperscript{6}
      i. As of 2009, approximately 368,000 people in Texas have HCV infection
      ii. Approximately 80% of cases are chronic infections

II. Disease course\textsuperscript{1,7-8}

III. Genotypes\textsuperscript{2,5-8}
   A. 6 genotypes have been identified
   B. Genotype 1
      i. Most common genotype in the United States (US) and western Europe
      ii. Accounts for 80% of HCV patients in the US

Figure 1. Disease Course of HCV.

Figure 2. Locations of Highest Incidence of HCV by Genotype.\textsuperscript{9} Source: ClevelandClinicMedED.com
I. Definitions of virologic response
   A. Rapid virologic response (RVR): undetectable viral load (VL) at week 4 of treatment
   B. Early virologic response (EVR): VL decreases by at least 2 log IU/mL from baseline at week 12 of treatment
   C. Extended rapid virologic response: undetectable VL at treatment weeks 4 and 12
   D. Sustained virologic response (SVR): VL remains undetectable 24 weeks following treatment cessation; considered to be synonymous with cure
   E. Null response: VL does not decrease by at least 2 log IU/mL by week 12 of treatment
   F. Partial response: VL decreases by at least 2 log IU/mL from baseline by week 12 of treatment, but still detectable at week 24 of treatment
   G. Virologic breakthrough: initially undetectable VL during treatment that becomes detectable despite continued treatment
   H. Relapse: VL is undetectable during treatment, but becomes detectable after treatment cessation

Figure 3. Virologic Response Terms. Source: hepatitis.va.gov

II. Factors affecting response to treatment

Figure 4. Variables Affecting Response to HCV Treatment.

III. Evolution of standard of care of treatment for HCV genotype 1
   A. Agents:
      i. Interferon (IFN)
      ii. Ribavirin (RBV)
      iii. Pegylated interferon (PegIFN)
      iv. Protease inhibitors (PI)
Figure 5. Development of HCV Treatment.

B. Development of HCV treatment (See Figure 5)
   i. 1991
      a. IFN
      b. Mean SVR rate in patients with genotype 1: ~5%
   ii. 1998
      a. Combination treatment of IFN and RBV
      b. Mean SVR rate in patients with genotype 1: ~30%
   iii. 2001
      a. IFN reformulated to PegIFN
      b. Combination treatment of PegIFN and RBV (“dual therapy”)
      c. Mean SVR rate in patients with genotype 1: 40-50%
   iv. 2011
      a. Addition of PI to PegIFN and RBV (“triple therapy”)
      b. Mean SVR rate in patients with genotype 1: 60-70%

C. Limitations of therapy with PegIFN and RBV²,¹⁶
   i. Unacceptable rate of SVR for patients with genotype 1 infection
   ii. Subcutaneous dosage form of PegIFN
   iii. Discontinuation in approximately 30% of patients due to lack of tolerability¹⁷
       a. Hemolytic anemia: 14%; neutropenia: 3-11%; thrombocytopenia: 1-8%
       b. Fatigue: 40-49%; myalgia: 32-42%
       c. Injection site reaction: 10-28%
       d. Headache: 35-48%
       e. Nausea: 24-29%; diarrhea: 14-16%
       f. Alopecia: 10-25%
       g. Depression: 17-22%

D. Direct-acting antiviral (DAA) agents: PI¹⁷-¹⁹ (See Appendix A)
   i. Available agents: telaprevir (TVR), boceprevir (BOC)
Figure 6. Results of Early Clinical Trials of TVR (on left) and BOC (on right) in Genotype 1 Treatment-Naïve and Treatment-Experienced Patients.20-26 (See Appendices B and C)

ii. Mechanism of action: inhibition of the nonstructural protein 3/4A (NS3/4A) protease necessary for HCV RNA replication and virion assembly

iii. Administration
   a. Must be administered with PegIFN and RBV
   b. TVR26,27
      1. Must be taken with at least 20 g of fat
      2. 2 tablets every 8 hours (6 tablets per day)
   c. Regimens for treatment-naïve patients and prior relapsers
      a) Undetectable VL at weeks 4 and 12
         1) Triple therapy (TT) for 12 weeks then dual therapy for 12 weeks
         2) 24 weeks total
      b) VL ≤1000 IU/mL at weeks 4 and/or 12
         1) TT for 12 weeks then dual therapy for 36 weeks
         2) 48 weeks total
   d. Regimen for prior partial and null responders
      a) TT for 12 weeks then dual therapy for 36 weeks
      b) 48 weeks total
   e. Regimens for treatment-naïve patients with compensated cirrhosis
      a) Undetectable VL at weeks 4 and 12
         1) TT for 12 weeks then dual therapy for 36 weeks
         2) 48 weeks total
   c. BOC27,28
      1. Must be taken with food
      2. 4 capsules every 8 hours (12 capsules per day)
      3. Lead-in period (LI) with PegIFN and RBV for 4 weeks
      4. Regimens for treatment-naïve patients
         a) Undetectable VL at weeks 8 and 24
            1) LI for 4 weeks then TT for 24 weeks
            2) 28 weeks total
         b) Detectable VL at week 8 and undetectable VL at week 24
            1) LI for 4 weeks then TT for 32 weeks then dual therapy for 12 weeks
            2) 48 weeks total
5. Regimens for prior partial responders and prior relapers
   a) Undetectable VL at weeks 8 and 24
      1) LI for 4 weeks then TT for 32 weeks
      2) 36 weeks total
   b) Detectable VL at week 8 and undetectable at week 24
      1) LI for 4 weeks then TT for 32 weeks then dual therapy for 12 weeks
      2) 48 weeks total
6. Regimens for null responders and patients with compensated cirrhosis
   a) LI for 4 weeks then TT for 44 weeks
   b) 48 weeks total
iv. Discontinuation of therapy
   a. Inadequate virologic response within a certain amount of time suggests unlikelihood of SVR
   b. Continuation of therapy in setting of poor response may trigger the development of treatment-emergent resistance
   c. Futility rules:
      1. TVR
         a) If VL > 1000 IU/mL at treatment week 4 or 12: discontinue triple therapy
         b) If detectable VL at treatment week 24: discontinue triple therapy
      2. BOC
         a) If VL > 100 IU/mL at treatment week 12: discontinue triple therapy
         b) If detectable VL at treatment week 24: discontinue triple therapy
v. Tolerability issues
   a. PegIFN and RBV remain the backbone of treatment
   b. Fatigue (TVR: 56%; BOC: 55-58%)
   c. Anemia (TVR: 36%; BOC: 45-50%)
   d. Nausea (TVR: 39%; BOC: 43-46%)
   e. Skin reactions (TVR: 56%; BOC: 16-17%)
vi. Patient populations in which use of these agents is off-label
   1. Patients with decompensated cirrhosis
   2. Patients coinfected with human immunodeficiency virus or hepatitis B virus
   3. *Liver transplant recipients*

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**IMPACT OF HCV ON LIVER TRANSPLANTATION**

I. HCV is the most common indication for liver transplantation 12,29-36
   A. ~31% of adult patients waiting for a liver transplant in the US
   B. ~26% of adult liver transplant recipients in the US listed HCV as the primary cause of their liver disease
   C. ~40% of liver transplant recipients at University Hospital are HCV-positive

II. Recurrence of HCV after liver transplantation 12-13,30,33-37
   A. If detectable HCV VL at time of transplant, VL becomes detectable within a few days after transplantation
   B. Accelerated rate of fibrosis progression
      i. 20-40% of transplant recipients with preexisting HCV develop cirrhosis within 5 years of transplant compared to 3-20% of immunocompetent patients who develop cirrhosis within 20 years
      ii. 30-42% risk of decompensation within 1 year of cirrhosis diagnosis for transplant recipients compared to less than 5% of immunocompetent patients
   C. HCV accounts for approximately two-thirds of graft failures 37-38
   D. Decreased rate of patient survival
      i. 3 year survival rate of transplant recipients that develop decompensated cirrhosis: 10%
      ii. 3 year survival rate of immunocompetent patients that develop decompensated cirrhosis: 60%
      iii. Rate of 5-year survival among liver recipients with HCV ~25% lower than those without HCV
TREATMENT OF HCV IN POTENTIAL LIVER TRANSPLANT CANDIDATES

I. Treatment goals\textsuperscript{12-13,16,30,36}
A. Achieve SVR
B. Improve liver disease
C. Prevent worsening of liver disease
D. Postpone need for transplantation
E. *Prevent recurrent HCV in the allograft following transplantation*\textsuperscript{*}

II. Eligibility for IFN-containing treatment regimens\textsuperscript{12-13,30,35-36,39}
A. Poor candidates
   i. Lack of tolerability likely
   ii. At high risk of complications: liver failure, infection, death
   iii. Examples:
      a. Patients with decompensated cirrhosis
      b. Patients with higher MELD scores
B. Ideal candidates
   i. Higher potential for tolerability of regimen
   ii. Preserved hepatic function
   iii. Examples
      a. Candidates with potential to receive a graft from a living donor
      b. Candidates with a MELD waiting list upgrade for hepatocellular carcinoma

III. Study by Everson et al.\textsuperscript{40}
A. Objective
   i. To evaluate the safety and efficacy of the pre-transplant administration of a low accelerating dose regimen of PegIFN and RBV for the prevention of HCV recurrence post-transplant
   ii. Post-transplant virologic response (PTVR): undetectable VL 12 weeks after transplant
   iii. Combined virologic response (CVR): undetectable VL 12 weeks after end of treatment
B. Patient population (n=79)
   i. Chronic HCV infection
      a. Genotype 1: n=44
      b. Genotype 2/3: n=32; genotype 4: n=2; genotype 6: n=1
   ii. Listed for liver transplantation with a predictably short time until transplantation
   iii. Likely to tolerate therapy
C. Multicenter randomized controlled trial
   i. Patients with genotypes 1, 4, and 6 randomized 2:1 to treatment:observation (n=31:n=16)
   ii. All patients with genotypes 2 and 3 received treatment (n=32)
   iii. Treatment consisted of a low accelerating dose regimen of PegIFN and RBV
D. Pertinent efficacy results
   i. 22\% (13/59) of treated patients achieved CVR compared to none of the untreated patients
   ii. 59\% (n=26/44) of treated transplant recipients achieved undetectable VL by the time of transplant
      a. 42\% (n=11/26) achieved PTVR
      b. 50\% (n=13/26) relapsed
      c. 8\% (n=2/26) died within 12 weeks after transplant
   iii. Response to varying treatment lengths
      a. <8 weeks of treatment
         1. 25\% (n=2/8) achieved undetectable VL at time of transplant
         2. None achieved PTVR
      b. 8 to 16 weeks of treatment
         1. 68\% (n=15/22) achieved undetectable VL at time of transplant
         2. 18\% (n=4/22) achieved PTVR
c. Greater than 16 weeks of treatment
   1. 64% (n=9/14) achieved undetectable VL at time of transplant
   2. 50% (n=7/14) achieved PTVR

E. Safety results
   i. 19% (n=11/59) of treated patients experienced cytopenias
   ii. 12% (n=7/59) of treated patients experienced infections
   iii. 5 treated patients and 2 untreated patients died before liver transplantation

F. Take home points
   i. Treatment with PegIFN and RBV prior to transplant can prevent post-transplant HCV recurrence in those most likely to tolerate therapy
      a. No PTVR achieved in patients receiving less than 8 weeks of treatment
      b. Treatment for greater than 16 weeks was associated with best rates of PTVR
   ii. Treatment is associated with risk of side effects
      a. Most notably cytopenias and infections
      b. Incidence of side effects may be increased among general liver transplant recipient population

IV. Phase 3 studies of TVR and BOC
   (See Appendix C)
   A. Patients with decompensated cirrhosis were not included
   B. SVR rates among cirrhotic patients
      i. Trials with TVR: 42-66% SVR in TVR groups compared to 10-33% SVR with PegIFN + RBV groups
      ii. Trials with BOC: 47-59% SVR in BOC groups compared to 0-38% SVR with PegIFN + RBV groups

V. CUPIC multicenter study in France: experience with triple therapy in setting of compensated cirrhosis
   A. Objective: to study the safety and efficacy of triple therapy with PI for at least 16 weeks
   B. Patient population (n=455)
      i. Compensated cirrhosis
      ii. Genotype 1 HCV
      iii. Non-responders, partial responders, relapsers
   C. Preliminary efficacy results: undetectable level of viral load
      i. Week 8 of treatment: 85% (n=224/265) on TVR; 37% (n=55/149) on BOC
      ii. Week 12 of treatment: 86% (n=219/254) on TVR; 61% (n=88/144) on BOC
      iii. Week 16 of treatment: 86% (n=177/205) on TVR; 71% (n=86/126) on BOC
   D. Preliminary safety results
      i. Infections in 8.8% (n=26/296) of TVR group; 2.5% (n=4/159) of BOC group
      ii. Asthenia in 4.7% (n=14/296) of TVR group; 5.7% (n=9/159) of BOC group
      iii. Serious adverse effects in 48.6% (n=144/296) of TVR group and 38.4% (n=61/159) of BOC group
      iv. 14.5% (n=43/296) of TVR group and 7.4% (n=12/159) of BOC group discontinued therapy due to adverse effects
   E. Take home points:
      i. PIs were associated with on-treatment virologic response in patients with compensated cirrhosis
         a. More patients reached an undetectable viral load with TVR than BOC
         b. Gap in virologic response between treatment groups narrowed as treatment duration increased
      ii. High rate of side effects in compensated liver dysfunction
      iii. High rate of discontinuation due to adverse effects with triple therapy

VI. Summary of pre-transplant treatment of HCV
   A. Limited literature in patients with compensated cirrhosis
   B. No literature on the use of triple therapy in patients with decompensated cirrhosis
   C. Treating with dual or triple therapy is difficult due to high rate of adverse effects and discontinuation
   D. Therapy resulting in undetectable VL at the time of transplant provides the patient with the best chance of avoiding recurrence following transplantation
TREATMENT OF HCV IN LIVER TRANSPLANT RECIPIENTS

I. Treatment goals
A. Achieve SVR
B. Maintain function and extend survival of transplanted graft
C. Extend patient survival

II. Dual therapy of PegIFN and RBV post-transplantation
A. SVR rates of 20-30% in transplant recipients with genotype 1
B. Tolerability
   i. Poses a major difficulty for this population due to propensity to develop anemia
   ii. Dose reduction required in 65-75% of patients
   iii. Approximately 25% of patients discontinue treatment due to adverse effects

III. Concerns of treatment with triple therapy in this population
A. Triple therapy not yet approved in liver transplant recipients
B. Increased risk of adverse effects and lack of tolerability
C. Concern for drug interactions between PI and backbone immunosuppressant agents cyclosporine (CsA) and tacrolimus (TAC)
   i. Calcineurin inhibitors (CNI) and mammalian target of rapamycin (mTOR) inhibitors
      a. Primarily metabolized by cytochrome P450 3A4 (CYP450 3A4)
      b. Substrates of P-glycoprotein (P-gp)
   ii. PI
      a. CYP450 3A4 substrates and inhibitors
      b. P-gp substrates and inhibitors

IV. Pharmacokinetic studies of PI with CNI
A. Healthy volunteers: 2 small studies

Table 1: Magnitude of Increase in CNI Pharmacokinetics After a Single Dose of TVR or BOC

<table>
<thead>
<tr>
<th>Protease Inhibitor</th>
<th>Cyclosporine</th>
<th>Tacrolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>AUC</td>
</tr>
<tr>
<td>TVR</td>
<td>1.35 fold</td>
<td>4.3 fold</td>
</tr>
<tr>
<td>BOC</td>
<td>2 fold</td>
<td>2.7 fold</td>
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</table>

V. Experiences using triple therapy in liver transplant recipients
<table>
<thead>
<tr>
<th>Study</th>
<th>response to prior HCV treatment</th>
<th>PI</th>
<th>CNI</th>
<th>change to CsA</th>
<th>CNI dose</th>
<th>CNI interval</th>
<th>efficacy results</th>
<th>safety results</th>
<th>take home points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pereira et al.</td>
<td>Unknown</td>
<td>TVR</td>
<td>TAC + EVL</td>
<td>No</td>
<td>TAC 0.5 mg; EVL 0.25 mg</td>
<td>Weekly (TAC); every 3 days (EVL)</td>
<td>Undetectable VL in 2 pts after 5 weeks of therapy and in 1 pt after 12 weeks of therapy</td>
<td>D/C of treatment in 1 pt due to skin rash and headache</td>
<td>Most centers combined TVR-based triple therapy with CsA</td>
</tr>
<tr>
<td>Rogers et al.</td>
<td>Pts 1 and 2: null-responders; Pt 3: partial-responder</td>
<td>TVR</td>
<td>TAC</td>
<td>No</td>
<td>Based on level; target level increased by 30%</td>
<td>BID changed to twice per week</td>
<td>Pt 1: achieved RVR, undetectable VL 4 months after therapy completion; Pt 2: null response; Pt 3: relapse</td>
<td>Worsening anemia requiring EPO in pts 1 and 2; pancytopenia resulting in D/C in pt 2; 1 pt without adverse effects</td>
<td>Patients studied were primarily treatment-experienced</td>
</tr>
<tr>
<td>Pungpapong et al.</td>
<td>3 null-responders; 3 partial-responders; 1 pt with poor tolerance</td>
<td>TVR</td>
<td>CsA</td>
<td>Yes</td>
<td>50-100% of original CsA dose</td>
<td>BID changed to daily</td>
<td>Undetectable VL: 17% of pts at week 4, 100% at week 12; acute rejection due to low CsA levels: 1 pt</td>
<td>Mild renal insufficiency due to CsA toxicity; cytopenias common; TVR D/C in 1 pt due to severe anemia; 5 pts required EPO; 2 pts required GCSF</td>
<td>TVR has a greater effect on TAC pharmacokinetics than CsA pharmacokinetics</td>
</tr>
<tr>
<td>Burton et al.</td>
<td>9 null-responders; 3 treatment-naïve pts</td>
<td>CsA</td>
<td>CsA</td>
<td>Yes</td>
<td>Reduced to 25% of total daily dose</td>
<td>Daily changed to every other day</td>
<td>Undetectable VL in 92% of pts at week 4; VL increased following decline in 2 pts; no acute rejection</td>
<td>3 pts hospitalized; 5 pts required blood; no episodes of rash</td>
<td>Required decreased TAC dose and extension of dosing interval to weekly or twice weekly dosing</td>
</tr>
<tr>
<td>Kwo et al.</td>
<td>Null-responders</td>
<td>CsA</td>
<td>CsA</td>
<td>Yes</td>
<td>Based on level</td>
<td>Based on level</td>
<td>Undetectable VL in 3 pts at week 12; 1 pt reached futility at week 4 but had undetectable VL at week 24</td>
<td>All required RBV dose reduction, EPO, GCSF, and blood; all with rash; 1 pt with perianal pain; all CsA levels in target range</td>
<td>Required decreased CsA dose and extension of dosing interval to daily or every other day</td>
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<tr>
<td>McCashland et al.</td>
<td>Unknown</td>
<td>TVR</td>
<td>CsA</td>
<td>Yes</td>
<td>Based on level</td>
<td>Based on level</td>
<td>Based on level</td>
<td>2 pts met futility rules at week 4; 2 pts achieved RVR; undetectable VL in all pts (3) completing 12 weeks of therapy; undetectable VL in 1 pt at week 24; no rejection</td>
<td>1 pt experienced a 2 log decrease in VL by day 19; 1 pt experienced delayed response</td>
</tr>
<tr>
<td>Schlitsky et al.</td>
<td>Pt 1: partial-responder Pts 2 and 3: null-responders</td>
<td>BOC</td>
<td>CsA</td>
<td>Unknown</td>
<td>Based on level</td>
<td>Based on level</td>
<td>1 pt attained undetectable VL and 1 pt experienced</td>
<td>Only fatigue experienced; no treatment D/C; no CsA toxicity</td>
<td></td>
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</table>

**Take Home Points**

- Most centers combined TVR-based triple therapy with CsA
- Patients studied were primarily treatment-experienced
- TVR has a greater effect on TAC pharmacokinetics than CsA pharmacokinetics
  - Required decreased TAC dose and extension of dosing interval to weekly or twice weekly dosing
  - Required decreased CsA dose and extension of dosing interval to daily or every other day
- Promising preliminary rates of viral response with triple therapy
- Lack of tolerability due to anemia and leukopenia is a concern
- Patients experiencing anemia and leukopenia required EPO and GSF

*Bid, twice daily; BOC, boceprevir; CsA, cyclosporine; D/C, discontinuation; EPO, erythropoietin; EVL, everolimus; pt, patient; GCSF, granulocyte colony-stimulating factor; TAC, tacrolimus; TVR, telaprevir; VL, viral load*
Table 3. Experience with TVR in Liver Transplant Recipients.52

<table>
<thead>
<tr>
<th>Study</th>
<th>Werner et al. Liver Transpl. 2012;18:1464-70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To study the feasibility of TVR-based triple therapy for HCV genotype 1 in liver transplant patients in terms of efficacy, drug-drug interactions, and safety</td>
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<tr>
<td>Study Design</td>
<td>Single center retrospective pilot study in Germany</td>
</tr>
<tr>
<td>Enrollment</td>
<td>9 consecutive patients being treated for the recurrence of HCV after liver transplantation</td>
</tr>
</tbody>
</table>

### Patient Population

- All HCV genotype 1
- Mean age: 60.9 years old
- Mean BMI: 27.1 kg/m²
- Mean time since liver transplant: 52 months (range: 2 – 168 months)
- Mean baseline HCV VL 6.64 log₁₀ IU/mL (range: 3.97 – 7.25 log₁₀ IU/mL)
- Table

### Baseline VL (log₁₀ IU/mL)

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<tr>
<td>IL28B Genotype</td>
<td>CT</td>
<td>CT</td>
<td>CT</td>
<td>CT</td>
<td>CT</td>
<td>TT</td>
<td>CT</td>
<td>CT</td>
<td>CT</td>
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<tr>
<td>Baseline VL (log₁₀ IU/mL)</td>
<td>3.97</td>
<td>5.53</td>
<td>6.58</td>
<td>6.97</td>
<td>6.58</td>
<td>7.25</td>
<td>5.89</td>
<td>5.53</td>
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### Compensated Liver Function

- Yes
- Yes
- Yes
- Yes
- Yes
- Yes
- No
- Yes

### Baseline Immunosuppressants

- TAC
- TAC+MMF
- TAC
- TAC+CCS
- SiR+CCS
- CsA+MMF+CCS
- CsA+MMF+CCS
- CsA

### Pre-Transplant HCV Treatment

- IFN+RBV (NR)*
- IFN+RBV+AMT (NR)*
- None
- PegIFN+RBV (NR)
- PegIFN+RBV (relapse)
- PegIFN+RBV (NR)
- PegIFN+RBV (NR)
- PegIFN+RBV (NRx2)*
- PegIFN+RBV (NR then TVR)
- PegIFN+RBV (breakthrough)

### Prior Post-Transplant HCV Treatment

- PegIFN+RBV (NR)*
- None
- PegIFN+RBV (NR)
- PegIFN+RBV (NR)
- PegIFN+RBV (relapse)
- PegIFN+RBV (NR)
- PegIFN+RBV (relapse)
- PegIFN+RBV (NRx2)*
- PegIFN+RBV (NR then TVR)
- PegIFN+RBV (breakthrough)

### HCV Treatment

- PegIFN + RBV + TVR x 12 weeks

### CNI Adjustment

- TAC and SiR were adjusted to a single weekly dose, while CsA was kept as a daily dose
- 22-fold reduction in TAC, 7-fold reduction in SiR, and 2.5-fold reduction in CsA

### Pharmacokinetic Analysis

- Trough levels of TAC, SiR, and CsA were above target range 28%, 45%, and 13%, respectively, of exposure time
- Trough levels of TAC, SiR, and CsA were below target range 32%, 54%, and 21%, respectively, of exposure time
- Trough levels of TAC, SiR, and CsA were within target range 40%, 1%, and 66%, respectively, of exposure time

### Efficacy Results

- Week 4: undetectable VL in 4 patients; VL close to LLOQ in patients 4, 8, 9
- Week 8: undetectable VL in 7 patients
- Week 12: undetectable VL in all except patient 4

### Safety Results

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<td>Blood Transfusion</td>
<td>2 units</td>
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<td>None</td>
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<td>2 units</td>
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<td>6 units</td>
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<td>GCSF Use</td>
<td>Yes</td>
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<td>RBV Reduction</td>
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<td>Reason for D/C</td>
<td>N/A</td>
<td>N/A</td>
<td>Side effects</td>
<td>Bacterial PNA</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

### Other

- 5 hospitalizations: bacterial PNA, TAC overdose with renal failure, Yersinia-induced enteritis, DM exacerbation, increased LFTs from NASH
- Hb <10 g/dL: 6 patients; Hb <8 g/dL: 4 patients; WBC <2500/µL: 6 patients; WBC <1500/µL: 3 patients; Plt <50,000/µL: 4 patients
- Mild skin reactions: 3 patients
- SCR increase >1.5 mg/dL: 3 patients

### Take Home Points

- Patient population included treatment-experienced individuals with poor response IL28B genotypes and compensated liver disease
- Most significant drug interaction between TVR and TAC; least difficulty in maintaining very narrow target immunosuppressant levels with CsA
- High rate of virologic response with triple therapy; 8 of 9 patients achieved undetectable VL by week 12 of treatment; SVR data unknown
- All patients on TAC and CsA experienced side effects; 6 of 9 patients experienced anemia and required EPO; 6 of 9 patients experienced leukopenia and 2 patients required GCSF

*then low-dose PegIFN; AMT, amantadine; MMF, mycophenolate mofetil; NASH, nonalcoholic steatohepatitis; NR, non-response; Plt, platelets; Scr, serum creatinine; SiR, sirolimus; TAC, tacrolimus; TVR, telaprevir; VL, viral load; WBC, white blood cells
Table 4: Experience with BOC in Liver Transplant Recipients.38

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To evaluate interactions and safety of BOC in HCV recurrence following liver transplantation</td>
</tr>
<tr>
<td>Study Design</td>
<td>Single center pilot study in France</td>
</tr>
<tr>
<td>Enrollment</td>
<td>5 consecutive patients</td>
</tr>
</tbody>
</table>

**Patient Population**
- All males with HCV genotype 1
- Mean age: 62.6 years old
- Mean BMI: 24.8 kg/m²
- Mean MELD score at baseline: 9.2
- Mean time since liver transplant: 48.6 months (range: 3 – 105 months)
- Mean baseline HCV VL: 6.87 log₁₀ IU/mL (range: 6.3 – 7.97 log₁₀ IU/mL)

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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</thead>
<tbody>
<tr>
<td>IL28B Genotype</td>
<td>CC</td>
<td>CT</td>
<td>CT</td>
<td>CC</td>
<td>TT</td>
</tr>
<tr>
<td>Baseline VL (log₁₀ IU/mL)</td>
<td>6.30</td>
<td>7.97</td>
<td>7.10</td>
<td>6.58</td>
<td>6.33</td>
</tr>
<tr>
<td>Baseline CNI</td>
<td>CsA 50 mg (AM); 25 mg (PM)</td>
<td>CsA 125 mg (AM); 100 mg (PM)</td>
<td>CsA 25 mg BID</td>
<td>TAC 1 mg daily</td>
<td>TAC 2 mg BID</td>
</tr>
<tr>
<td>Other Baseline Immunosuppressants</td>
<td>Prednisone 5 mg daily</td>
<td>Prednisone 5 mg daily</td>
<td>MMF 500 mg BID</td>
<td>EVL 0.5 mg BID</td>
<td>None</td>
</tr>
<tr>
<td>Response to Previous HCV Treatment</td>
<td>Relaper</td>
<td>NR</td>
<td>Treatment-naïve</td>
<td>Relaper</td>
<td>NR</td>
</tr>
<tr>
<td>HCV Treatment</td>
<td>PegIFN + RBV x 4 weeks → PegIFN + RBV + BOC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main Immunosuppressant Dose at Week 12</td>
<td>CsA 25 mg BID</td>
<td>CsA 75 mg (AM); 50 mg (PM)</td>
<td>CsA 25 mg BID</td>
<td>TAC 0.5 mg 2 days in 3</td>
<td>TAC 0.5 mg daily</td>
</tr>
<tr>
<td>Pharmacokinetic Analysis</td>
<td>Reduction in clearance: CsA (~50%); TAC (~80%); EVL: (~52%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy Results: Virologic Response</td>
<td>Week 4: mean decrease in VL of 2.2 log₁₀ IU/mL (range: 0.62 – 4.3 log₁₀ IU/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety Results</td>
<td>Anemia experienced by all of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Take Home Points</td>
<td>Patient population primarily included treatment-experienced individuals with low MELD scores and poor response IL28B genotypes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BOC, boceprevir; CNI, calcineurin inhibitor; CsA, cyclosporine; EPO, erythropoietin; EVL, everolimus; Hb, hemoglobin; NR, non-response; RBV, ribavirin; TAC, tacrolimus; VL, viral load
VI. Take home points gained from published experiences
   A. Triple therapy can be safely utilized in transplant recipients for the treatment of HCV
      i. Promising preliminary results in difficult-to-treat population
      ii. Most results published are not in terms of SVR, but are presented in terms of EVR
      iii. Close therapeutic drug monitoring of immunosuppressant medications is essential
      iv. High risk for severe anemia and leukopenia
   B. PI choice
      i. Published experiences primarily with TVR
      ii. Less significant effect on the pharmacokinetics of CNI expected with BOC
   C. CNI choice
      i. Published experience primarily with CsA
      ii. Less pronounced pharmacokinetic effect expected with CsA
      iii. Less difficulty maintaining target level with CsA
      iv. More ease with new dosing schedule of CsA compared with new dosing schedule of TAC
      v. Potential benefit to switching patients managed on TAC to CsA prior to PI initiation

CONCLUSIONS

I. Triple therapy is an option for the treatment of HCV after liver transplantation

II. Pertinent patient characteristics to consider
   A. Prior treatment experience
   B. IL28B genotype
   C. Current viral load and stage of fibrosis
   D. Expected ability to tolerate therapy

III. Treat patients with rapidly progressive fibrosis or high viral load
   A. If on TAC, consider switch to CsA or decrease TAC to once weekly dosing
   B. If on CsA, decrease dose by 30-50%
   C. Frequently monitor therapeutic drug levels of CsA or TAC
   D. Monitor for anemia, leukopenia, skin rash, rejection, kidney dysfunction, and infection
   E. Be prepared for patient requiring EPO and/or GCSF

IV. Consider postponing treatment in stable patients
   A. Continue to monitor viral load
   B. Continue to monitor measures of fibrosis
   C. Consider starting treatment upon the arrival of new agents to market

FUTURE DIRECTIONS

I. Therapy changes in the pipeline
   A. Future agents
      i. Numerous agents at different stages of development
      ii. Expected arrival to market as early as 2013 – 2014
      iii. Examples: daclatasvir, asunaprevir, sofosbuvir, ABT450/r, ABT333, ABT267
   B. IFN-free regimens to minimize side effects and increase probability of tolerability
II. Effect of new agents on treatment decisions
   A. Expectations
      i. Decrease in potential for drug interaction
      ii. Similar to PI in percentage of patients attaining SVR
   B. Decision to treat with BOC or TVR
      i. Decreased risks involved with postponing HCV treatment
      ii. Drug interaction potential
      iii. Increased difficulty of monitoring
      iv. Risk of limiting future treatment options

III. Possible expansion of literature
   A. Size of studies
   B. Patient population
      i. Decompensated cirrhosis
      ii. Liver transplant recipients
      iii. Patients with co-infections
REFERENCES

## APPENDICES

### Appendix A

<table>
<thead>
<tr>
<th>Generic (Brand Name)</th>
<th>Telaprevir (Incivek®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Vertex Pharmaceuticals, Inc.</td>
</tr>
<tr>
<td>Dosage Forms</td>
<td>375 mg tablet</td>
</tr>
<tr>
<td>FDA-Approved Indication: Treatment of HCV genotype 1 in combination with PegIFN alfa and ribavirin in adult patients with compensated liver disease</td>
<td></td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Metabolism: hepatic (CYP3A4)</td>
</tr>
<tr>
<td></td>
<td>Protein binding: 59-76%</td>
</tr>
<tr>
<td></td>
<td>Half-life: 9-11 hours at steady state</td>
</tr>
<tr>
<td></td>
<td>Tmax: 4-5 hours</td>
</tr>
<tr>
<td></td>
<td>Elimination: Feces (82%); Urine (1%)</td>
</tr>
<tr>
<td>Dosing</td>
<td>750 mg PO every 8 hours</td>
</tr>
<tr>
<td>Administration</td>
<td>With food containing ≥20 g of fat</td>
</tr>
<tr>
<td>Most Common Adverse Effects</td>
<td>Fatigue (56%), anemia (36%), nausea (39%), rash (56%), pruritus (47%)</td>
</tr>
</tbody>
</table>

### Appendix B: Phase 2 Studies

#### PROVE-1 Trial

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Genotype 1; treatment-naive; no evidence of decompensated liver disease or cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group</td>
<td>PegIFN α-2a + RBV for 48 weeks and placebo for the first 12 weeks</td>
</tr>
<tr>
<td>(n=75)</td>
<td>41% achieved SVR 11% of patients discontinued treatment due to adverse effects</td>
</tr>
<tr>
<td>Experimental Group 1</td>
<td>PegIFN α-2a + RBV for 24 weeks and TVR for the first 12 weeks</td>
</tr>
<tr>
<td>(n=79)</td>
<td>61% achieved SVR 21% of patients discontinued treatment due to adverse effects</td>
</tr>
<tr>
<td>Conclusion</td>
<td>The addition of TVR significantly improved SVR rates in treatment-naive patients with genotype 1 HCV</td>
</tr>
</tbody>
</table>

#### PROVE-2 Trial

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Genotype 1; treatment-naive; no evidence of cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group</td>
<td>PegIFN α-2a + RBV for 48 weeks and placebo for the first 12 weeks</td>
</tr>
<tr>
<td>(n=85)</td>
<td>46% achieved SVR</td>
</tr>
<tr>
<td>Experimental Group 1</td>
<td>PegIFN α-2a + RBV + TVR for 12 weeks</td>
</tr>
<tr>
<td>(n=84)</td>
<td>60% achieved SVR</td>
</tr>
<tr>
<td>Experimental Group 2</td>
<td>PegIFN α-2a + RBV for 24 weeks and TVR for the first 12 weeks</td>
</tr>
<tr>
<td>(n=83)</td>
<td>69% achieved SVR</td>
</tr>
<tr>
<td>Experimental Group 3</td>
<td>PegIFN α-2a + TVR for 12 weeks</td>
</tr>
<tr>
<td>(n=82)</td>
<td>36% achieved SVR</td>
</tr>
<tr>
<td>Conclusion</td>
<td>Triple therapy with TVR significantly improved SVR rates in treatment-naive patients with genotype 1 HCV</td>
</tr>
</tbody>
</table>

### Appendix C: Phase 3 Studies

#### ADVANCE Trial

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Genotype 1; treatment-naive; no evidence of decompensated liver disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group</td>
<td>PegIFN α-2a + RBV for 48 weeks and placebo for the first 12 weeks</td>
</tr>
<tr>
<td>(n=365)</td>
<td>44% achieved SVR 33% (n=7/21) of cirrhotics achieved SVR</td>
</tr>
<tr>
<td>Experimental Group 1</td>
<td>TVR for 12 weeks</td>
</tr>
<tr>
<td>(n=365)</td>
<td>PegIFN α-2a + RBV for 24 weeks if VL was undetectable at weeks 4 and 12</td>
</tr>
<tr>
<td></td>
<td>89% achieved SVR</td>
</tr>
<tr>
<td></td>
<td>PegIFN α-2a + RBV for 48 weeks if VL was detectable at week 4 or week 12</td>
</tr>
<tr>
<td></td>
<td>54% achieved SVR</td>
</tr>
<tr>
<td>Experimental Group 2</td>
<td>TVR for 8 weeks and placebo for 4 weeks</td>
</tr>
<tr>
<td>(n=365)</td>
<td>PegIFN α-2a + RBV for 24 weeks VL was undetectable at weeks 4 and 12</td>
</tr>
<tr>
<td></td>
<td>83% achieved SVR</td>
</tr>
<tr>
<td></td>
<td>PegIFN α-2a + RBV for 48 weeks if VL was detectable at week 4 or week 12</td>
</tr>
<tr>
<td></td>
<td>50% achieved SVR</td>
</tr>
<tr>
<td>Conclusion</td>
<td>Triple therapy with TVR was associated with significantly improved SVR rates in treatment-naive patients with genotype 1 HCV with most patients receiving 24 total weeks of therapy</td>
</tr>
</tbody>
</table>
**ILLUMINATE Trial**

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Genotype 1; treatment-naïve; no evidence of decompensated liver disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n=162)</td>
<td>PegIFN α-2a + RBV for 24 weeks and TVR for the first 12 weeks</td>
</tr>
<tr>
<td></td>
<td>Extended rapid virologic response: PegIFN α-2a + RBV for 24 more weeks</td>
</tr>
<tr>
<td></td>
<td>No additional therapy after 24 weeks</td>
</tr>
<tr>
<td></td>
<td>92% achieved SVR</td>
</tr>
<tr>
<td></td>
<td>82% (n=31/38) of cirrhotics achieved SVR</td>
</tr>
<tr>
<td>Group 2 (n=160)</td>
<td>Extended rapid virologic response: PegIFN α-2a + RBV for 24 more weeks</td>
</tr>
<tr>
<td></td>
<td>No extended rapid virologic response: PegIFN α-2a + RBV for 24 more weeks</td>
</tr>
<tr>
<td></td>
<td>88% achieved SVR</td>
</tr>
<tr>
<td></td>
<td>88% (n=29/33) of cirrhotics achieved SVR</td>
</tr>
<tr>
<td>Group 3 (n=118)</td>
<td>PegIFN α-2a + RBV for 24 more weeks</td>
</tr>
<tr>
<td></td>
<td>64% achieved SVR</td>
</tr>
<tr>
<td></td>
<td>55% (n=23/55) of cirrhotics achieved SVR</td>
</tr>
</tbody>
</table>

**Conclusion**

Triple therapy with TVR for 12 weeks followed by therapy with Peg-IFN and RBV for 12 weeks was noninferior to triple therapy for 12 weeks followed by dual therapy for 24 weeks in terms of SVR rates in treatment-naïve patients with genotype 1 HCV.

---

**REALIZE Trial**

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Genotype 1; did not achieve SVR to 1 previous course of PegIFN + RBV; no evidence of decompensated liver disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group</td>
<td>PegIFN α-2a + RBV for 48 weeks</td>
</tr>
<tr>
<td>(n=133)</td>
<td>17% achieved SVR</td>
</tr>
<tr>
<td></td>
<td>10% (n=1/10) of cirrhotics achieved SVR</td>
</tr>
<tr>
<td>Experimental Group 1 (n=266)</td>
<td>PegIFN α-2a + RBV for 48 weeks and TVR for the first 12 weeks</td>
</tr>
<tr>
<td></td>
<td>64% achieved SVR</td>
</tr>
<tr>
<td></td>
<td>44% (n=11/25) of cirrhotics achieved SVR</td>
</tr>
<tr>
<td>Experimental Group 2 (n=264)</td>
<td>PegIFN α-2a + RBV for 48 weeks and TVR for weeks 5-16</td>
</tr>
<tr>
<td></td>
<td>66% achieved SVR</td>
</tr>
<tr>
<td></td>
<td>40% (n=10/25) of cirrhotics achieved SVR</td>
</tr>
</tbody>
</table>

**Conclusion**

Regardless of the presence of a lead-in phase, the addition of TVR significantly improved SVR rates in patients with genotype 1 HCV who had a previous relapse, a partial response, or no response to previous treatment.

---

**SPRINT-2 Trial**

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Genotype 1; treatment-naïve; no evidence of decompensated liver disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group</td>
<td>PegIFN α-2a + RBV + placebo for 44 more weeks</td>
</tr>
<tr>
<td>(n=133)</td>
<td>38% achieved SVR</td>
</tr>
<tr>
<td></td>
<td>38% (n=9/24) of cirrhotics achieved SVR</td>
</tr>
<tr>
<td>Experimental Group 1 (n=266)</td>
<td>PegIFN α-2a + RBV + BOC for 24 more weeks</td>
</tr>
<tr>
<td></td>
<td>PegIFN α-2a + RBV + placebo for 20 more weeks</td>
</tr>
<tr>
<td></td>
<td>No additional therapy after 28 weeks</td>
</tr>
<tr>
<td></td>
<td>96% achieved SVR</td>
</tr>
<tr>
<td></td>
<td>41% (n=14/34) of cirrhotics achieved SVR</td>
</tr>
<tr>
<td>Experimental Group 2 (n=264)</td>
<td>PegIFN α-2a + RBV + BOC for 44 more weeks</td>
</tr>
<tr>
<td></td>
<td>PegIFN α-2a + RBV + placebo for 20 more weeks</td>
</tr>
<tr>
<td></td>
<td>No additional therapy after 52 weeks</td>
</tr>
<tr>
<td></td>
<td>66% achieved SVR</td>
</tr>
<tr>
<td></td>
<td>52% (n=22/42) of cirrhotics achieved SVR</td>
</tr>
</tbody>
</table>

**Conclusion**

The addition of BOC significantly improved SVR rates in treatment-naïve patients with genotype 1 HCV, with similar rates among groups of 24 and 44 weeks of BOC.

---

**RESPOND-2 Trial**

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Genotype 1; previous treatment for HCV; no evidence of decompensated liver disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group</td>
<td>PegIFN α-2a + RBV + placebo for 44 more weeks</td>
</tr>
<tr>
<td>(n=180)</td>
<td>21% achieved SVR</td>
</tr>
<tr>
<td></td>
<td>0% (n=0/10) of cirrhotics achieved SVR</td>
</tr>
<tr>
<td>Experimental Group 1 (n=162)</td>
<td>PegIFN α-2a + RBV + BOC for 32 more weeks</td>
</tr>
<tr>
<td></td>
<td>PegIFN α-2a + RBV + placebo for 20 more weeks</td>
</tr>
<tr>
<td></td>
<td>No additional therapy after 36 weeks</td>
</tr>
<tr>
<td></td>
<td>59% achieved SVR</td>
</tr>
<tr>
<td></td>
<td>35% (n=6/17) of cirrhotics achieved SVR</td>
</tr>
<tr>
<td>Experimental Group 2 (n=161)</td>
<td>PegIFN α-2a + RBV + BOC for 44 more weeks</td>
</tr>
<tr>
<td></td>
<td>PegIFN α-2a + RBV + placebo for 20 more weeks</td>
</tr>
<tr>
<td></td>
<td>No additional therapy after 24 weeks</td>
</tr>
<tr>
<td></td>
<td>66% achieved SVR</td>
</tr>
<tr>
<td></td>
<td>77% (n=17/22) of cirrhotics achieved SVR</td>
</tr>
</tbody>
</table>

**Conclusion**

The addition of BOC significantly improved SVR rates in previously treated patients with genotype 1 HCV.