Safety of Treatment in Cirrhotics in the Era of New Antiviral Therapies for Hepatitis C Virus

JEFFREY NADELSON MD, ALAN EPSTEIN MD, THOMAS SEPE MD

BOSTON UNIVERSITY SCHOOL OF MEDICINE
ROGER WILLIAMS MEDICAL CENTER

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Hepatitis C Virus (HCV)

- Hepatitis C (HCV) is a flavivirus related to Yellow Fever and West Nile Virus.
- Most common chronic blood-borne infection in the U.S.
- Cirrhosis develops in 25-30% of patients infected with HCV.
- Most common indication for adult liver transplantation in U.S.
Natural History of HCV Infection

**Acute Hepatitis C**
- Exposure
  - HCV RNA Detectable
  - Elevated ALT
  - HCV Antibody Detectable

**Chronic Hepatitis C**
- 70%-80% Clearance or Persistence
- ~25% Chronic Progressors
- Cirrhosis
- Liver Cancer 1-4% per year

Timeline:
- 1-2 weeks
- 2-6 weeks
- 4-8 weeks
- 24 weeks
- 15-30 years
Hepatitis C Progression

Fibrosis & Disease Progression in Hepatitis C. Marcellin, et al. Hepatology, 2002
Original Hepatitis C Treatment

- PEG-Interferon
  - Increases expression of proteins that interfere with Hep C viral replication

- Ribavirin
  - Enhances the antiviral effect of interferon
  - Precise mechanism of action uncertain

- Treatment lasts for one year; if successful, induces cure
Side Effects of IFN and Ribavirin

- **INTERFERON:**
  - Hematologic complications
    - neutropenia, thrombocytopenia
  - Neuropsychiatric complications
    - memory and concentration disturbances, visual disturbances, headaches, depression, irritability
  - Metabolic complications
    - hypothyroidism, hyperthyroidism, low-grade fever
  - Gastrointestinal complications
    - nausea, vomiting, weight loss
  - Pulmonary complications
    - Interstitial fibrosis

- **RIBAVIRIN:**
  - Hematologic complications
    - hemolytic anemia
  - Reproductive complications
    - birth defects
  - Metabolic complications
    - gout
New Hepatitis C Treatments Available

- FDA recently approved two new NS3/4A protease inhibitors for treatment of Hep C in 2011
  - Boceprevir (Victrelis)
  - Telaprevir (Incivek)
- Are added to, do not replace, original therapy
- Indications:
  - Treatment of chronic Hep C genotype 1
  - With compensated liver disease, including cirrhosis
  - Previously untreated or who have failed previous interferon and ribavirin therapy
Challenges of Telaprevir Therapy

- Cannot be given alone or resistance will develop

- Same side effects plus additional side effects:
  - Anemia
  - Neutropenia
  - Thrombocytopenia
  - Severe Rash

- Logistical Challenges:
  - Must be given at same time every day
  - Must be given with fatty food (e.g., ice cream)
  - Cost: 12 weeks of telaprevir is $52,644 per patient
Goals of HCV Therapy

- **Primary Goal**
  - Eradicate HCV Infection

- **Secondary Goal**
  - Slow disease progression
  - Improve histology
  - Reduce risk of hepatocellular carcinoma
  - Improve health-related quality of life
Why Examine Cirrhotics undergoing HCV Antiviral Therapy?

Reasons:
• Never been studied before
• Need better understanding of what to expect and how to better treat these complex and medically challenging patients.

Study Objective:
• To review and compare the safety profile of current antiviral treatment in cirrhotic vs. non-cirrhotic patients
Methods

- Type of Study
  - IRB-approved retrospective chart review

- Institutions Participating in Providence, RI.
  - Roger Williams Medical Center
  - University Gastroenterology

- Data Collected
  - Hepatitis C serologies, basic demographic data, liver biopsy results, adverse events, ribavirin dose reductions, and reasons for treatment discontinuation
Study Population

- **Patient Sample**
  - 34 cirrhotic patient charts reviewed
    - Currently undergoing HCV triple antiviral therapy with telaprevir
  - 2 Institutions
  - January 1, 2011 - January 1, 2013

- **Data Analysis**
  - Our HCV cirrhotic data set was compared to non-cirrhotics from a phase 3 study sponsored by Vertex Pharmaceuticals
Phase 3 Non-Cirrhotic Data Published in NEJM

- Title: Telaprevir for Previously Untreated Chronic Hepatitis C Virus Infection (ADVANCE Trial) (ClinicalTrials.gov NCT00627926)

- Randomized, double blind, phase 3 study conducted to evaluate the efficacy and safety of telaprevir-based therapy among patients who had received no previous treatment for HCV infection.

- Used as control for our study

Anemia Definition in Phase 3 Study

- Hemoglobin levels of at least 12 g per deciliter in the case of women or 13 g per deciliter in the case of men.

- Reduction Criteria:
  - Hemoglobin <10 g/dL in patients with no cardiac disease
  - Decrease in hemoglobin of ≥2 g/dL during any 4 week period in patients with history of stable cardiac disease
Reasons for Discontinuation of Treatment in Phase 3 Trial

- Grade 3 rash (severe, involving more than 50% of the body surface, or rash with the appearance of substantial systemic signs or symptoms).

- Hemoglobin <8.5 g/dL in patients with no cardiac disease, or Hemoglobin <12 g/dL despite 4 weeks at reduced dose in patients with history of stable cardiac disease.
Approved Medications and Dosages

- **Telaprevir:** 750mg po Q8H
- **Ribavirin:** 600mg po BID *(can be adjusted based upon comorbidities)*
- **Pegylated Interferon:** 180 micrograms SubQ injection weekly
Antiviral Therapy Schedule

If HCV RNA > 1000 IU/ml → stop therapy
If HCV RNA detectable → stop therapy
Basic Demographics

- 34 patients with liver cirrhosis identified over a 2 year period
  - Mean age: 56 years
  - 74% were men
  - 88% were genotype 1a
  - Avg. HCV viral load: 3,909,804 IU/mL
Ethnicities

- Caucasian: 70%
- African-American: 15%
- Hispanic: 14%
- Other: 1%
Identification of Cirrhosis

- 76% Non-Invasive Diagnostic Imaging
- 24% Liver Biopsy
Dose Reductions of Ribavirin at Start of Treatment

- 10 (30% of total) patients were prescribed reduced dosages of ribavirin at onset of treatment.
# Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Cirrhotics (%)</th>
<th>Phase 3 Study (Non-Cirrhotics (%))</th>
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<tbody>
<tr>
<td>Anemia</td>
<td>91</td>
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<tr>
<td>Thrombocytopenia</td>
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<td>Skin Rash</td>
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<td>Fatigue</td>
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<td>Rectal Burning</td>
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<tr>
<td>Insomnia</td>
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<td>32.23</td>
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<tr>
<td>Visual Disturbances</td>
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<td>7.99</td>
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</tbody>
</table>
Dose Reductions of Ribavirin During Treatment

- 100% of the dose reductions of ribavirin during treatment were due to symptomatic anemia.
Reasons for Treatment Discontinuation

- Anemia: 8% (Our Data in Cirrhotics), 4% (Phase 3 Data in Non-Cirrhotics)
- Severe Skin Rashes: 6% (Our Data in Cirrhotics), 2% (Phase 3 Data in Non-Cirrhotics)
- Psych Manifestations: 15% (Our Data in Cirrhotics)
Conclusion

Dose reductions of ribavirin during treatment due to anemia
- Cirrhotics: 47%
- Non-cirrhotics: 19%

Discontinuation of Treatment
- Anemia:
  - Cirrhotics 8% vs. 4% in non-cirrhotics
- Severe Skin Rashes:
  - Cirrhotics 6% vs. 2% in non-cirrhotics
Treatment of HCV with telaprevir-containing regimens in cirrhotics, as compared with non-cirrhotics, was associated with a higher incidence of adverse events such as rash and anemia.

Undertaking HCV antiviral therapy in cirrhotics is very complex and should be further explored on a national or international level to better understand what to expect and how to better treat these complex and medically challenging patients.
Coming Soon....

- What is the efficacy rate of telaprevir in cirrhotic patients compared to non-cirrhotics?

- Sustained virologic response (SVR) rates for the same 34 cirrhotic patients undergoing triple anti-viral therapy with telaprevir.
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Any Questions??
Jeff.nadelson@gmail.com