Hepatitis C: Overview, Treatment, & Transplantation

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Outline

- Overview of the Hepatitis C (HCV) virus
- Transplantation for HCV
- Treatment of HCV
- Hepatocellular carcinoma and HCV
Hepatitis C Virus Overview

- Discovered in 1989
  - Principal cause of “non-A, non-B hepatitis”
- RNA Virus
  - Flavivirus
Diagnosis of Hepatitis C Virus

- Diagnosed through blood test
- Six Major Genotypes
  - Genotype 1 (subtypes a & b) most common in the US
  - Genotypes 2-3 (also subtypes a & b) next common
  - Genotypes 4-6 rare in the US
Hepatitis C Virus
Incidence

- One of the major leading causes of chronic liver disease.
- An estimated 180 million people are infected worldwide.
- In the US, between 1999-2002 the prevalence was 1.6%, approximately 4.1 million persons.


*Per 100,000 population.
†Until 1995, acute hepatitis C was reported as acute hepatitis non-A, non-B.

Risk Factors

- Intravenous Drug Use
- Intranasal Drug Use
- Blood Transfusion
  - Rare since 1990
- Hemodialysis
- Nosocomial
- Sexual
- Organ Transplant
- Perinatal Transmission
  - Approximately 5%
- Piercings/Tattoos
- Injuries
Screening

- Up to 75% of the 4 million Americans infected with HCV are unaware they are infected
- Screening tests
  - Anti-HCV Antibody
  - HCV RNA PCR

Screening Recommendations

• IV drug use
• Recipients of blood transfusions or organ transplants prior to July 1992
• Persons with the following medical conditions:
  – HIV infection
  – Hemophilia
  – Hemodialysis
  – Unexplained abnormal liver chemistry tests
Screening Recommendations (cont’d)

• Children born to Hep C infected mothers
• Health care or other persons after needle stick injury or mucosal exposure to Hep C infected blood
• Current sexual partners of Hep C infected persons
Liver Biopsy

• Used to determine extent of liver damage
• Grade / Stage
  – Grade = extent of necroinflammatory injury
  – Stage = extent of fibrosis / presence of cirrhosis
Development of Cirrhosis

• 5-25% persons develop cirrhosis over 25-30 years

• Accelerated by:
  – Obesity
  – Older age
  – Immunosuppression
  – Concomitant alcohol usage
Disease Course

Natural History of HCV Infection

Exposure Acute Phase
- 15-40% Resolved
- 60-85% Chronic

Cirrhosis
- 20% progression
- ~20 year progression rate accelerated with HIV, alcohol

ESLD
- 4%/yr

HCC
- 3-4%/yr

Transplant/death

Time (yr)
- 10
- 20
- 30

HCC = hepatocellular carcinoma
ESLD = end-stage liver disease
Coexisting/Concurrent Liver diseases

• Alcohol
  – Strong association with alcohol use and progression of liver fibrosis
  – Alcohol interferes with response to treatment
  – Increased risk for HCC

• NASH (fatty liver) / Obesity
  – Plays a role in progression of fibrosis & response to treatment

Burden of Disease

- Leading cause of liver transplantation in the United States
- Leading cause of liver related mortality
  - ~12,000 deaths annually
- A leading cause of Hepatocellular Carcinoma (HCC)

Kim WR. Hepatology 2002;36(Suppl):S30-S34
### Primary Disease of Patients Receiving Liver Transplants: 2011 Data

<table>
<thead>
<tr>
<th>Primary Disease</th>
<th>UWHC</th>
<th>Region</th>
<th>US</th>
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<tbody>
<tr>
<td>Acute Hepatic Necrosis</td>
<td>5.5</td>
<td>5.0</td>
<td>4.8</td>
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<tr>
<td>Non-Cholestatic Cirrhosis</td>
<td>54.8</td>
<td>48.3</td>
<td>55.6</td>
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<tr>
<td>Cholestatic Liver Disease/Cirrhosis</td>
<td>11</td>
<td>7.9</td>
<td>8.4</td>
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<tr>
<td>Biliary Atresia</td>
<td>2.7</td>
<td>3.7</td>
<td>2.9</td>
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<tr>
<td>Metabolic Diseases</td>
<td>6.8</td>
<td>4.6</td>
<td>3.4</td>
</tr>
<tr>
<td>Malignant Neoplasms</td>
<td>19.2</td>
<td>23.4</td>
<td>19.7</td>
</tr>
<tr>
<td>Other</td>
<td>0.0</td>
<td>7.0</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Transplantation: Outcomes

- Effect on graft survival is controversial
- Some studies have shown decreased 1, 3, and 5 year graft survival
- Others have shown similar survival
- Improved with better HCC screening
- Retransplantation outcomes convincingly worse
• Study out of Norway from 2007:
  – Two hundred and fifty-three (90%) patients received a first liver allograft. HCC was found in 38% of the explanted livers. Survival at 1, 3 and 5 years was 82%, 69% and 61% vs. 85%, 80% and 76% for the comparison group (p<0.0001), this survival difference was also evident when excluding patients with HCC (p=0.007). HCV patients with HCC had 1, 3 and 5 year survival of 73%, 52% and 46% compared with 88%, 80% and 71% for the HCV patients without HCC (p=0.0005).

• Study out of University of Penn looking at SRTR database from 1992-1998
  – Liver transplantation in HCV-positive recipients was associated with an increased rate of death (hazard ratio, 1.23; 95% confidence interval [CI], 1.12-1.35) and allograft failure (hazard ratio, 1.30; 95% CI, 1.21-1.39), as compared with transplantation in HCV-negative recipients.

Hepatitis C impairs survival following liver transplantation irrespective of concomitant hepatocellular carcinoma
Espen Melum, Styrbjom Friman, Kristian Bjørøe, Allan Rasmussen, Helena Isoniemi, Henrik Gjertsen, Lars Bäckman, Antti Oksanen, Michael Olausson, Frans F. Duraj, Bo-Göran Ericzon

Transplantation: Outcomes

• King’s College UK
  – Cumulative survival rates for the 149 patients with HCV infection were 79 percent after one year, 74 percent after three years, and 70 percent after five years, as compared with rates of 75 percent, 71 percent, and 69 percent, respectively, in the HCV-negative transplant recipients (P=0.12).

• Mayo Clinic
  – Cumulative patient survival for HCV-infected recipients was similar to that of recipients transplanted for chronic non-B-C hepatitis, or alcoholic and metabolic liver disease, better than that of patients transplanted for malignancy or hepatitis B (P = .02 and P = .003, respectively), and significantly worse than that of patients transplanted for cholestatic liver disease (P = .001).

Transplantation: Outcomes

- Acceleration of cirrhosis when compared to immune competent persons
- 5 year rate of cirrhosis 10-20%
- At least 10% require retransplant for recurrent disease

Recurrent Hepatitis C

- Incidence: >95%
- Risk factors:
  - Donor factors: Age
  - Genotype
  - Viral level
  - Immunosuppression
Post Transplant Management

- Monitor Hepatitis C viral levels
- Surveillance liver biopsies
- Balance immunosuppression carefully
  - May switch to cyclosporine
  - Steroids?
- Consider antiviral therapy
Antiviral therapies for HCV

- Interferon mono therapy was first available treatment. SVR was 12%
- Pegylated interferon & Ribavirin therapy improved side effects with pegylated formulation & improved SVR rates
- Protease inhibitors came on the market in April 2011
Treatment Goals

- Prevent death from Hepatitis C infection
- Reduce risk for Hep C related complications
  - HCC
  - Cryoglobulinemia
- Achieve Sustained virologic response (SVR)
- Decrease fibrosis
Measuring response

- **Sustained Virologic Response (SVR)**
  - Nondetectable 24 weeks after completion of therapy
- **End of Treatment Response (ETR)**
  - Nondetectable virus but relapse occurs
- **Rapid virological response (RVR)**
  - Undetectable HCV RNA at 4 weeks of treatment
  - Predicts high likelihood of SVR
- **Early virological response (EVR)**
  - Used to identify nonresponders
  - Failure to decrease HCV RNA by 2 logs or more at week 12 strongly predicts nonresponse (97-100%)
  - Not as good at predicting SVR
Predicting Response to Treatment

- Genotype
- Viral load
- IL28B genetic test
- Age
- Race
- Gender
- Obesity
- Insulin resistance/diabetes
- Cirrhosis
To Treat or Not to Treat: Considerations

- Genotype: virus, patient (IL28B)
- Personal plans (marriage, pregnancy)
- Patient mindset
- Extrahepatic features (fatigue)
- Stage of Fibrosis and lifetime risk of cirrhosis
- Age
- Liver function
- HIV coinfection
- Duration of infection
- Family and other support
- Occupation
- Contraindications & comorbidities; insulin resistance
Standard Treatment

- Genotypes 1&4
  - Pegylated interferon & Ribavirin for 48 weeks
- Genotypes 2-3
  - Pegylated interferon & ribavirin for 24 weeks
Pegylated Interferon

Pegasys® or Peg Intron®
- Taken by injection
- Pegasys standard dose 180 mcg weekly
- Peg Intron is weight based, standard dose is 1.5 mcg/kg/week

Helps fight the virus in two ways:
- Helps healthy cells defend themselves against the virus
- Strengthens the immune system, which helps to stop the virus from growing in number
• Ribavirin is a pill that is taken twice a day with food

• Weight based for Genotype 1
  – 800 mg for patients <65 kg
  – 1000 mg for patients 65-85 kg
  – 1200 mg for patients 85-105 kg
  – 1400 mg for patients >105 kg
Side Effects of therapy

- Fatigue
- Flu like symptoms including body aches, low grade fever, etc.
- Headache
- Depression
- Insomnia
- Induce or worsen pre-existing autoimmune disorders (thyroid disease, psoriasis)
- Renal toxicity
Side effects of therapy (cont’d)

• Hemolytic anemia
• Severe neutropenia
• Thrombocytopenia

• Growth factors are used to combat these side effects
Contraindications

- Renal disease
- Pregnancy
- History of solid organ transplant (heart, lung, kidney)
- Uncontrolled depression
- Autoimmune hepatitis
- Untreated thyroid disease
- Severe heart failure, coronary heart disease, or COPD
Limitations of PEG-IFN/R

• Limited efficacy (low SVR rate)
  – Genotype 1: 30-40%
  – Genotype 2: 70-80%
  – Genotype 3: 60-70%

• Lower effectiveness in difficult-to-treat populations:
  – African-Americans
  – Bridging fibrosis/cirrhosis

• Long duration of treatment
• Requires high adherence
• Contraindicated in may people
• Substantial adverse side effects
Protease inhibitors

- Boceprevir and telaprevir
- Became available April 2011
- Approved for GT 1 non treated patients AND previous nonresonders
### TVR in Treatment-Naïve Patients

![Graph showing patients with SVR (%)](image)

<table>
<thead>
<tr>
<th></th>
<th>eRVR+</th>
<th>eRVR-</th>
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<tbody>
<tr>
<td>T12PR 24</td>
<td>92%</td>
<td>24%</td>
</tr>
<tr>
<td>T12PR 48</td>
<td>87%</td>
<td></td>
</tr>
<tr>
<td>T12PR 48</td>
<td>64%</td>
<td></td>
</tr>
<tr>
<td>&lt;20 weeks</td>
<td>23%</td>
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</tbody>
</table>

- **Δ = 4.5%**
- **(2-sided 95% CI = -2.1% to +11.1%)**

**N =**
- 149/162
- 140/160
- 76/118
- 23/100

*Sherman et al. NEJM 2011*
BOC in Treatment-Naïve Patients

Poordad et al. NEJM 2011
Benefits of Protease Inhibitors

- Improved SVR rates in genotype 1 patients (63-75%)
- Shortened duration of therapy without sacrificing SVR
- Efficacy in prior relapses and partial responders to PEG-IFN/R treatment
  - 69-88% in relapsers
  - 54-59% in partial responders
  - 29-33% in null responders
- Improved efficacy in patients with cirrhosis, African-Americans
- Minimal relapse rate and development of resistance when used appropriately: no dose reduction or interruption allowed

Jacobson et al. NEJM 2011
Sounds great, but…..

• Large pill burden (minimum 11-12 pills per day)
• TID dosing for PI, BID for RBV
• Requires high degree of adherence; rapid emergence of resistance
• Substantial adverse effects
• Requires intense monitoring
• Very expensive
• Complicated
• Clinical workload for administration
• Still need interferon
• Numerous drug/drug interactions
• Viral resistance
• Expensive!!!
Adverse Effects

- Rash: 41-60%
  - 90% mild-moderate, 6% severe
  - 3 cases of SJS, 11 cases DRESS syndrome reported
- Anemia
- Anorectal (discomfort, hemorrhoids, pruritus)
- Pruritus
- Nausea
- Neutropenia
- Altered taste
- Dry skin
- Diarrhea
Treatment PRE Transplantation

Most patients have already attempted & failed

Risky due to:

• Severe decompensation
• Cytopenias
• Sepsis

Ability to decrease viral load may improve post transplant survival
Treatment POST Transplant

• Extremely complicated due to side effects of therapy
  – Anemia, neutropenia, thrombocytopenia
  – Rejection
  – Infection
  – Drug-drug interactions
Challenges of Triple Therapy Post Transplant

• Anemia – Even more pronounced with protease inhibitors

• Drug interactions:
  – Both protease inhibitors impact the levels of drugs metabolized by the CYP3A/4 pathway
  – Protease inhibitors significantly increase the levels of cyclosporine and tacrolimus

On the Horizon

• Number of new classes of anti-HCV drugs in preclinical, early and late clinical development

• Different treatment strategies being tested
  – Interferon based, Interferon sparing
  – Shorter duration of therapy

• Preliminary results are encouraging
Curing HCV

- HCV Infection
  - HCV Diagnosis
    - HCV Treatment
      - Sustained Viral Response (HCV Cure)
Future Areas to Address

• Areas of need not adequately addressed
  – Prior Treatment failures
  – Post-transplant population
Hepatocellular Carcinoma

• Incidence
  – 4th most common cancer in the world
  – 28,720 new cases estimated to be diagnosed in the US in 2012 and 20,550 deaths

• Hepatitis C is a leading cause

• Successful treatment of HCV decreases risk for HCC


Kim WR. Hepatology 2002;36(Suppl):S30-S34

Hepatitis C impairs survival following liver transplantation irrespective of concomitant hepatocellular carcinoma


Verna & Brown (2012). UpToDate

Sherman et al. NEJM 2011

Poordad et al. NEJM 2011

Jacobson et al. NEJM 2011


Predictors of patient and graft survival following liver transplantation for hepatitis C.


http://www.srtr.org/csr/current/Centers/centerdetail