Hepatitis C: The new era of screening and treatment

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Objectives

• Describe the natural history of HCV infection
• Be able to diagnose HCV
• Know the factors which predict progression to fibrosis and cirrhosis
• Know that HCV therapy is rapidly changing, and that most patients now have > 95% cure rate with 8-12 weeks of oral therapy
• Understand the genomic organization of the HCV as it relates to new direct acting antivirals
• Contemplate that this breakthrough ranks with the development of treatment for syphilis, TB, and HIV

History of HCV diagnosis and screening

• Post-transfusion hepatitis: as HBsAg discovered and screened we had:
  – Non-A, Non-B hepatitis (NANB)
• Identification and cloning of virus 1989
• Testing for blood supply 1992
• Screening recommendations 2013

Worldwide prevalence of chronic HCV

More people have HCV than HIV!

Distribution of HCV genotypes

The risk of HCV from blood transfusion
Routes of transmission

**Acute HCV infection**

Take home point: perhaps 15% or more of patients infected recover without treatment. They generally remain anti-HCV positive.

**Chronic HCV infection**

Take home point: Chronic HCV is diagnosed by persistent presence of HCV RNA. Once you have made this dx, there is no need to test for RNA outside of treatment.

**Long term consequences of HCV infection and risk of cirrhosis**

Genotype 3 is only viral factor to affect progression. We don’t know slope of progression beyond 20 years.

**The history of the natural history of HCV (1968-2009)**

Take home points: Infection at older age, male sex, post-transfusion infection, co-infection with HBV/HIV, heavy alcohol use, NASH, obesity, insulin resistance linked to more likely progression. A majority of patients may not develop significant fibrosis. Better means to assess fibrosis (other than bx) would be very valuable to assess individual patients.

**More Americans die of HCV than HIV**


CDC screening recommendations

- Persons for whom HCV testing is recommended:
  - Individuals during 1945 through 1965 should be tested once (without prior ascertainment of HCV risk factors).
  - HCV testing is recommended for those who:
    - Currently inject drugs
    - Have a history of injecting drugs, including those who injected once or a few times many years ago
    - Have received medical transfusions before 1987
    - Have a history of clotting factor concentrates produced before 1987
    - Have a history of long-term hemodialysis
    - Have persistently abnormal alanine aminotransferase (ALT) levels
    - Have HIV infection
    - Have a history of transfusions or organ transplants, including persons who:
      - Were notified that they received blood from a donor who later tested positive for HCV infection
      - Received a transfusion of blood, blood components or an organ transplant before July 1992
  - HCV testing based on a recognized exposure is recommended for:
    - Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood
    - Children born to HCV-positive women

- Note: For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended.

What good is eradication of the virus?

- Stops progression to fibrosis/cirrhosis
- Stops development of portal hypertension in cirrhotic patients
- Decreases risk of hepatoma development
- Eliminates effects of type II cryoglobulinemia (renal injury, skin rash, neuropathy)
- Effect on risk of diabetes, lymphoma, fatigue
- Should reduce transmission to others

Improved outcomes with SVR

**SVR = Sustained viral response**

From HCVGuidelines.org

**Goal of treatment**

- The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by an SVR.

**Rating:** Class I, Level A

**Recommendations for pretreatment assessment**

- An assessment of the degree of hepatic fibrosis, using noninvasive testing or liver biopsy, is recommended.

**Rating:** Class I, Level A

**Recommendations for repeat liver disease assessment**

- Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred.

**Rating:** Class I, Level C

**Settings of Liver-Related Complications and Extrahepatic Disease in Which HCV Treatment is Most Likely to Provide the Most Immediate and Impactful Benefits**

**Highest Priority for Treatment Owing to Highest Risk for Severe Complications**

- Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4)
  **Rating:** Class I, Level A

- Organ transplant
  **Rating:** Class I, Level B

- Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (eg, vasculitis)
  **Rating:** Class I, Level B

- Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis
  **Rating:** Class IIa, Level B

**The HCV genome and viral proteins**
Brief history of treatment

- Interferon: Initially 3 MU TIW (very difficult)
- Interferon with ribavirin
- PEG interferon: weekly injection
- First generation protease inhibitors (Pis) (2011)
- PIs were first direct acting antiviral (DAA)- drug directed specifically against a viral enzyme/protein
- The explosion of treatment (2013 onward)

Treatment of NANB hepatitis up to 2011

- Initially (mid 1970's) steroids- reduced ALT
- IFN tested based on responses of HBV in 1986

Effect of first generation protease inhibitors

- Effect of DAAs on GT 1 responses
  - DAA= boceprevir or telaprevir
  - PEG= PEG-IFN
  - RBV = ribavirin

What do the DAAs do?

- Current DAAs:
  - Simeprevir
  - Ledipasvir
  - Sofosbuvir

2013: The Introduction of IFN-Free HCV Therapy

- PEG-IFN
- R, RBV = ribavirin

SOF= sofosbuvir
Evidence of drug effectiveness: SOF+ Ledipasvir in treatment-naïve, non-cirrhotic patients

Table 1: Response during and after Treatment.

<table>
<thead>
<tr>
<th>Response</th>
<th>LDV-SOF Rx 8 Wks (N=211)</th>
<th>LDV-SOF + RBV Rx 4 Wks (N=234)</th>
<th>LDV-SOF Rx 12 Wks (N=216)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR12 (%)</td>
<td>90/100</td>
<td>95/100</td>
<td>91/100</td>
</tr>
<tr>
<td>GT1b</td>
<td>100/100</td>
<td>100/100</td>
<td>100/100</td>
</tr>
<tr>
<td>GT1a without Q80K</td>
<td>90/100</td>
<td>85/100</td>
<td>80/100</td>
</tr>
</tbody>
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Evidence of drug effectiveness: SOF+ Ledipasvir in IFN +/- protease inhibitor failures

Table 2: Response during and after Treatment.

<table>
<thead>
<tr>
<th>Response</th>
<th>LDV-SOF Rx 12 Wks (N=211)</th>
<th>LDV-SOF + RBV Rx 12 Wks (N=211)</th>
<th>LDV-SOF Rx 24 Wks (N=188)</th>
<th>LDV-SOF + RBV Rx 24 Wks (N=190)</th>
</tr>
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<td>SVR12 (%)</td>
<td>90/100</td>
<td>90/100</td>
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Evidence of drug effectiveness: SOF+ Ledipasvir in treatment-naïve patients

Patients were previously untreated, GT1, 16% cirrhosis (well compensated)

Evidence of drug effectiveness: SOF+ Ledipasvir in IFN +/- protease inhibitor failures

Patients with GT1 HCV, ~20% cirrhosis; did not include those who withdrew from Rx
**Direct-Acting Antiviral Agents: Key Characteristics**

<table>
<thead>
<tr>
<th>NS3/4A Protease Inhibitors (PI)</th>
<th>NS5A Inhibitors</th>
<th>NS5B Nucleos(t)ide Inhibitors (NI)</th>
<th>NS5B Nonnucleoside Inhibitors (NNI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High potency</td>
<td>Intermediate potency</td>
<td>Intermediate potency</td>
<td>Limited genotypic coverage</td>
</tr>
<tr>
<td>Limited genotypic coverage</td>
<td>Pangenotypic coverage</td>
<td>Pangenotypic coverage</td>
<td>Low barrier to resistance</td>
</tr>
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<td>High barrier to resistance</td>
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<td>Low barrier to resistance</td>
</tr>
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**Genotype 1 Choices**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Regimen Options</th>
<th>SVR</th>
<th>Cost per SVR</th>
</tr>
</thead>
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<tr>
<td>Naïve, no cirrhosis</td>
<td>Wait until 2015</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>SOF/Peg-IFN/RBV x 12</td>
<td>92%</td>
<td>$114,500</td>
</tr>
<tr>
<td></td>
<td>SOF/RBV x 24 wks</td>
<td>~68%</td>
<td>$266,176</td>
</tr>
<tr>
<td>Naïve, cirrhosis</td>
<td>SOF/Peg-IFN/RBV x 12</td>
<td>80%</td>
<td>$131,675</td>
</tr>
<tr>
<td></td>
<td>SOF/Simeprevir x 12</td>
<td>&gt;90%</td>
<td>$169,800</td>
</tr>
<tr>
<td>Treatment experienced, no cirrhosis</td>
<td>Wait until 2015</td>
<td>?</td>
<td>?</td>
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**Cost effectiveness studies**


CONCLUSION: Sofosbuvir + pegIFN/RBV yields more favorable future health and economic outcomes than current treatment regimens for patients across all levels of treatment experience and cirrhosis stage, as well as for individuals with or without HIV co-infection. (and is lowest one year cost per SVR).

UCLA group
Current limitations

- HCV Genotypes 5, 6, 7
- Decompensated cirrhosis
- Patients with renal failure
- Ability to determine who should be treated sooner, which means...

Staging fibrosis

- “Noninvasive tests to stage the degree of fibrosis in patients with chronic HCV infection include models incorporating indirect serum biomarkers (routine tests), direct serum biomarkers (components of the extracellular matrix produced by activated hepatic stellate cells), and vibration-controlled transient liver elastography. No single method is recognized to have high accuracy alone and each test must be interpreted carefully. A recent publication of the Agency for Healthcare Research and Quality found evidence in support of a number of blood tests; however, at best they are only moderately useful for identifying clinically significant fibrosis or cirrhosis.”

Noninvasive assessment of fibrosis

- Detecting liver fibrosis and cirrhosis important!
- Even liver biopsy may have up to 24% false negative for cirrhosis (but it is still the gold standard)
- Fib4 score: based on AST, ALT, platelets and age
- Note: interpretation varies between HCV and NASH; not validated for other disorders.

Non-invasive markers of fibrosis

- “An FIB-4 index < 1.45 had a negative predictive value of 95% to exclude severe fibrosis with a sensitivity of 74%. An FIB-4 index higher than 3.25 had a positive predictive value to confirm the existence of a significant fibrosis (F3-F4) of 82% with a specificity of 98%. Using these ranges, 73% of the 847 liver biopsies were correctly classified.”
- Thus, ¾ of patients correctly classified.

Fibroscan, aka transient elastography

Based on speed of transmission of a sound wave impulse; transformed into a measure of liver stiffness, which is related to fibrosis.

Fibroscan

<table>
<thead>
<tr>
<th>CAP (dBm)</th>
<th>Median</th>
<th>V (m/s)</th>
<th>Median</th>
<th>E (kPa)</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>198</td>
<td>214</td>
<td>1,10</td>
<td>1,26</td>
<td>4,8</td>
<td></td>
</tr>
<tr>
<td>IQR</td>
<td>22</td>
<td>10%</td>
<td>IQR</td>
<td>0,9</td>
<td></td>
</tr>
<tr>
<td>IQR/med</td>
<td></td>
<td></td>
<td>IQR/med</td>
<td>15%</td>
<td></td>
</tr>
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</table>

Elasticated Liver stiffness is calculated using the formula $E = \frac{V^2}{3\cdot C}$ and assumes that liver tissue is isotropic, linear, and purely elastic with a density of 1.05 g/cm³. The values for both wave speeds and Young’s modulus are relative indices, and they should not be used alone. Absolute values for these measurements may vary among measurement devices from different manufacturers. ESI median is defined as the value which corresponds to the stiffness median.
Performance of CT in dx cirrhosis


- CT, MRI and US examinations of 142 patients with chronic liver disease who underwent surgery for complicated hepatocellular carcinoma (<3 cm in diameter) in 10 institutions were blindly reviewed in a multicenter study by three radiologists experienced in CT, MRI and US. The images were evaluated for five imaging parameters (irregular or nodular liver surface, blunt liver edge, liver parenchymal abnormalities, liver morphological changes and manifestations of portal hypertension) using a severity scale.

- RESULTS: The predictive diagnostic accuracy, sensitivity and specificity in discriminating LC from CH based on the best predictive signs were 72, 77 and 68% by CT; 68, 68 and 68% by MRI, and 66, 38 (lower than CT and MRI, p =0.001) and 89% (higher than CT and MRI, p =0.001) by US. According to the imaging impression scoring system, diagnostic accuracy, sensitivity and specificity were 67, 84 and 53% by CT; 70, 87 and 54% by MRI, and 64, 52 (lower than CT and MRI, p <0.0001) and 74% (higher than CT and MRI, p <0.003) by US.

- Take home: These patients were largely (91%) Childs A. CT only predicts cirrhosis in this group 2/3 of the time: a normal CT doesn’t exclude cirrhosis.
- Abnormalities become more pronounced as liver disease progresses

Summary

- HCV is a huge, global public health problem
- Modern genome-based (DAAs) therapy can cure the vast majority of patients without the side effects of interferon and with few side effects
- New therapies are successful in treatment failures and early cirrhosis

Considerations for therapy

- Avoidance of risky behavior; address alcohol abuse as well as IV and sexual exposure
- Genotype of the virus
- Prior treatment failure
- Presence of cirrhosis (and is it decompensated?)
- Co-infection: HBV, HIV

Effect of genotype on SVR

GT 2 and 3 can be treated for 24 weeks
Initial RNA viral load affected responses

Effect of viral load

[Graphs showing the effect of genotype and viral load on SVR]
Structure of the virus
Have to know the genes to understand the drugs!