Making a Decision on Whether to Initiate Treatment

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Outline

- Indications for treatment
- Contraindications to treatment
- Patient readiness
- Timing of treatment
Indications for Treatment
Indications for Protease Inhibitor (PI)-Based Triple Therapy

- Chronic hepatitis C virus (HCV) genotype 1
- Fulfill criteria for peginterferon alfa (PegIFN) and ribavirin (RBV) therapy
  - Well-controlled psychiatric disease
  - No autoimmune diseases
  - Able to tolerate significant anemia
  - Not considering pregnancy
- If cirrhosis, should be well compensated
  - No variceal hemorrhage, ascites, encephalopathy
- Ability to adhere to treatment goals and monitoring

Liver Disease Staging in Decision Making

- Liver biopsy remains the gold standard
- Noninvasive serum tests (eg, HCV FibroSURE)
  - Reasonable accuracy at the extremes of histologic fibrosis
- Transient elastography (FibroScan)
  - FDA cleared April 2013
  - Excellent positive predictive value, negative predictive value for cirrhosis
- Magnetic resonance imaging (MRI) elastography
What Can Be Learned From a Biopsy?

- Severity of HCV
  - Degree of inflammation
  - Stage of fibrosis
- Presence of other suspected findings (if you look)
  - Steatosis, nonalcoholic steatohepatitis, alcoholic steatohepatitis
  - Alpha-1 antitrypsin
  - Autoimmune hepatitis
- Presence of unsuspected findings
  - Granulomatous processes
  - Other
Noninvasive Markers of Fibrosis: Serum Markers

Fibrosis stage

FibroTest

Expected Fibrosis

0.75-1.00 F4
0.73-0.74 F3-F4
0.59-0.72 F3
0.49-0.58 F2
0.32-0.48 F1-F2
0.28-0.31 F1
0.22-0.27 F0-F1
0.00-0.21 F0

total bilirubin, alpha 2 macroglobulin, haptoglobin, gamma-glutamyl transpeptidase (GGT), and apolipoprotein A1

Elastography: FibroScan

The probe induces an elastic wave through the liver.

The velocity of the wave is evaluated in a region located from 2.5 cm to 6.5 cm below the skin surface.
Fibroscan Meta-Analysis

- Meta-analysis of 50 studies assessed the overall performance of FibroScan for diagnosing liver fibrosis

- The areas under the receiver operating characteristic curve were:
  - For significant fibrosis: 0.84 (95% CI, 0.82–0.86)
  - For severe fibrosis: 0.89 (95% CI, 0.88–0.91)
  - For cirrhosis: 0.94 (95% CI, 0.93–0.95)
Contraindications to Treatment
Contraindications to Therapy

- **Contraindications to PegIFN**
  - Uncontrolled neuropsychiatric disease (depression)
  - Autoimmune disease (systemic lupus erythmatosus, sarcoid, autoimmune hepatitis)
  - Cytopenias
  - Decompensated cirrhosis

- **Contraindications to RBV**
  - Anemia
  - Hemolytic conditions (eg, thalassemia)
  - Pregnancy
  - Renal failure
Patient Readiness
Patient Readiness: Considerations Before Beginning Triple Therapy

- Is this patient a good candidate for PegIFN and RBV?
- Are there any potential drug-drug interactions?
- Pill burden, food and fat effect with PIs
- What are the chances of sustained virologic response (SVR)?
  - Naive
  - Treatment-experienced
- How will we apply response-guided algorithms? Can duration be shortened?
- What are the risks of treating? Not treating?
- How will we manage adverse events?
  - Prepare for the possibility of temporary hardship
Preparation for Treatment: Evaluation of Drug-Drug Interactions

- Boceprevir (BOC) and telaprevir (TVR) are CYP3A4 inhibitors
  - Drug interactions may affect blood levels of either HCV PI or a coadministered drug
- Caution is needed with all coadministered medications
  - Review FDA approved label information for interaction lists
  - Reconcile patient medication list
  - Patient needs to communicate new meds started by other health care providers
  - Other resources: hcvadvocate.org; hep-druginteractions.org

Back D. 7th International Workshop on HIV & Hepatitis Co-infection; June 1-3, 2011; Milan, Italy. Lecture. AUC = area under the curve; CYP = cytochrome P450
## Lipid Lowering Agent DDIs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction Potential</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>Highly dependent on 3A4</td>
<td>Do not coadminister</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Highly dependent on 3A4</td>
<td>Do not coadminister</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td><strong>TVR caused AUC/Cmax ↑ 7.88/10.6</strong></td>
<td>Do not coadminister with TVR</td>
</tr>
<tr>
<td></td>
<td><strong>BOC caused AUC/Cmax ↑ 2.3/2.7</strong></td>
<td>With BOC: titrate dose carefully, do not exceed 20mg daily</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Not extensively metabolized by 3A4</td>
<td>Use with caution; monitor for myopathy</td>
</tr>
<tr>
<td></td>
<td><strong>BOC caused AUC/Cmax ↑ 1.6/1.5</strong></td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Not extensively metabolized by 3A4, but unexpected increases were seen with HIV PIs</td>
<td>Use with caution; monitor for myopathy</td>
</tr>
<tr>
<td>Fibrates</td>
<td>No clinically significant interaction expected (theoretical)</td>
<td>OK to coadminister</td>
</tr>
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</table>

Antihypertensive DDIs

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
<th>Interaction Potential</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibitors</td>
<td>lisinopril, ramipril, benazepril, enalapril</td>
<td>No CYP metabolism</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Diuretics</td>
<td>HCTZ, chlorthalidone, furosemide, bumetanide</td>
<td>No CYP metabolism</td>
<td>No adjustment</td>
</tr>
<tr>
<td>ARBs</td>
<td>losartan, valsartan, candesartan, irbesartan, telmisartan, olmesartan</td>
<td>Irbesartan and losartan metabolized by 3A4</td>
<td>Consider dose ↓ with irbesartan and losartan</td>
</tr>
<tr>
<td>Beta-Blockers</td>
<td>atenolol, carvedilol, metoprolol, propranolol, timolol, nabivolol</td>
<td>Carvedilol and nabivolol metabolized by 3A4</td>
<td>Consider dose ↓ with carvedilol and nabivolol</td>
</tr>
<tr>
<td>CCBs</td>
<td>amlodipine, nifedipine, felodipine, verapamil, diltiazem</td>
<td>Highly reliant on CYP3A for metabolism</td>
<td>Consider dose ↓ of amlodipine with TVR</td>
</tr>
</tbody>
</table>

ACE = angiotensin converting enzyme; ARB = angiotensin II receptor inhibitors; CCB = calcium channel blockers; HCTZ = hydrochlorothiazide

Patient Education is a Linchpin of HCV Management

- **HCV transmission**
  - Review CDC recommendations including sexual transmission

- **Avoid pregnancy during and for 6 months after RBV-based therapy**
  - 2 forms of barrier contraception (oral contraceptive pill levels fall with PIs)

- **Primary care hepatology**
  - Achieve and/or maintain a normal body mass index
  - Avoid alcohol
  - HIV, HBV testing
  - HAV, HBV immunization
  - HCC screening for advanced fibrosis
  - Variceal screening for cirrhosis

HAV = hepatitis A virus; HBV = hepatitis B virus; HCC = hepatocellular carcinoma
Pros

- PIs substantially increase chance of SVR across all patient groups including naive and treatment-experienced
- PIs shorten duration of therapy in many with response-guided therapy
- Successful treatment improves morbidity and mortality

Cons

- Complicated regimens, challenging adverse effects, and DDIs
- Likelihood of response related to PegIFN responsiveness
- Risk of resistance if therapy fails: impact on future options?
- Suboptimal response rates or limited or no data in several populations
  - HCV/HIV coinfection, transplant, decompensated cirrhosis
Multiple Factors in the Mix

- HCV Genotype
- Fibrosis Stage
- IL28B genotype
- Personal Plans (marriage, pregnancy)
- Age
- Family and Other Support
- Patient Attitude
- ALT
- Occupation
- Extrahepatic Features (fatigue, cryoglobulins)
- HIV Coinfection
- Contraindications

The New Therapy Pipeline
Timing of Treatment
Timing of Therapy

- Liver disease stage, symptoms or patient preference should guide treatment decisions
  - Deferral of therapy is reasonable for patients with minimal liver disease
  - Initiation of therapy with advanced fibrosis
- Deferral increasingly an option for more advanced stage disease as all-oral, highly potent direct-acting antiviral (DAA) regimens loom
Indications and contraindications for triple therapy are similar to those for prior PegIFN and RBV regimens.

Staging of liver disease is a key factor in decision to treat, as threshold to start is rising with newer DAAs on the horizon.

Many other factors influence the decision to start triple therapy.

More intensive education required regarding adherence, adverse effect monitoring, and DDIs.
End

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