Making a Decision on Whether to Initiate Treatment

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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)

Friedrich-Rust et al. *Gastroenterology.* 2008; 134:960–974

Contraindications to Treatment

Contraindications to Therapy

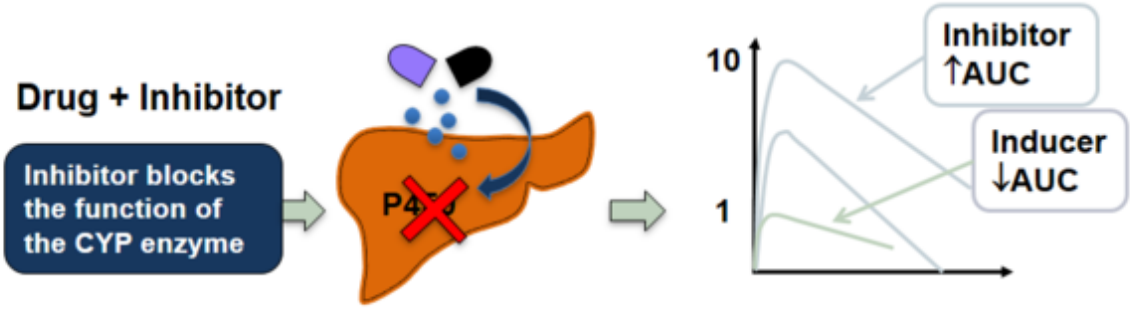
- Contraindications to PegIFN
  - Uncontrolled neuropsychiatric disease (depression)
  - Autoimmune disease (systemic lupus erythmatosus, sarcoid, autoimmune hepatitis)
  - Cytopenias
  - Decompensated cirrhosis
- Contraindications to RBV
  - Anemia
  - Hemolytic conditions (eg, thalassemia)
  - Pregnancy
  - 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 <u>all</u> 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

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

Kiser JJ et al. *Hepatology*. 2012 May;55(5):1620-8. DDI = drug-drug interaction

Antihypertensive DDIs

Class	Drugs	Interaction Potential	Recommendation
ACE Inhibitors	lisinopril, ramipril, benazepril, enalapril	No CYP metabolism	No adjustment
Diuretics	HCTZ, chlorthalidone, furosemide, bumetanide	No CYP metabolism	No adjustment
ARBs	losartan, valsartan, candesartan, irbesartan, telmisartan, olmesartan	Irbesartan and losartan metabolized by 3A4	Consider dose ↓ with irbesartan and losartan
Beta-Blockers	atenolol, carvedilol, metoprolol, propranolol, timolol, nabivolol	Carvedilol and nabivolol metabolized by 3A4	Consider dose ↓ with carvedilol and nabivolol
CCBs	amlodipine, nifedipine, felodipine, verapamil, diltiazem	Highly reliant on CYP3A for metabolism **Amlodipine AUC/Cmax ↑ 2.79/1.27 by TVR**	Consider dose ↓ of amlodipine with TVR

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

Kiser JJ et al. *Hepatology*. 2012 May;55(5):1620-8.

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

Treatment Decisions for HCV PIs: What We've Learned Thus Far

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

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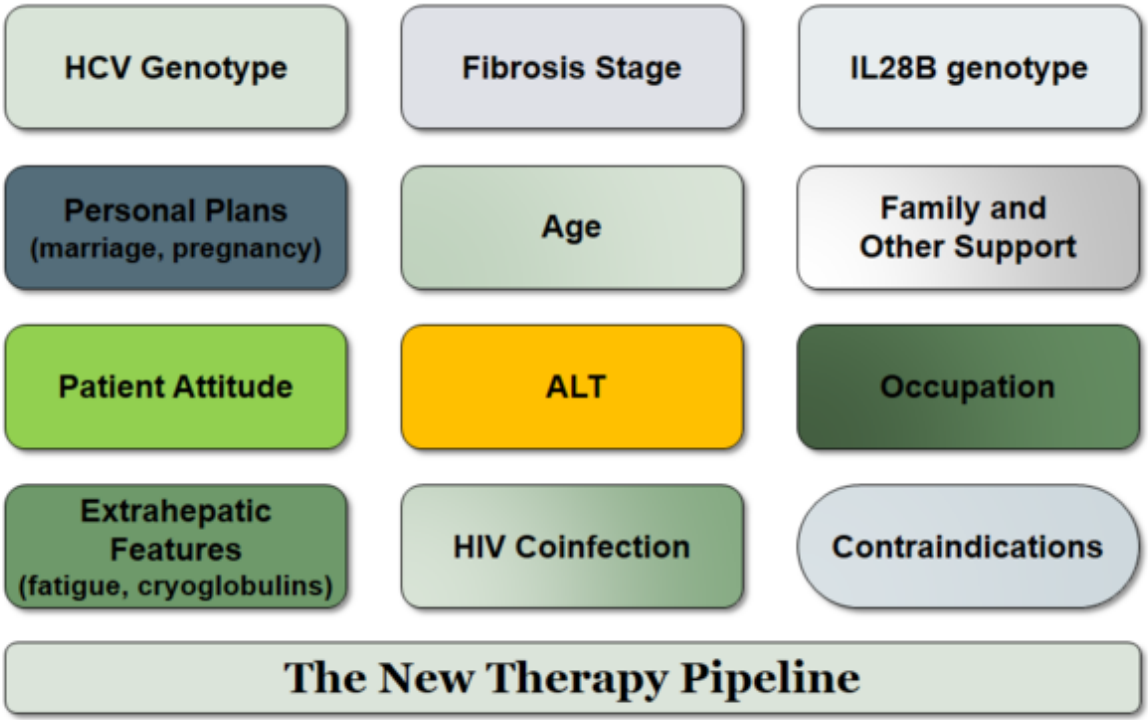
Multiple Factors in the Mix



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

Summary

- 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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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

Boceprevir [package insert]. May 2011; Telaprevir [package insert]. March 2012.

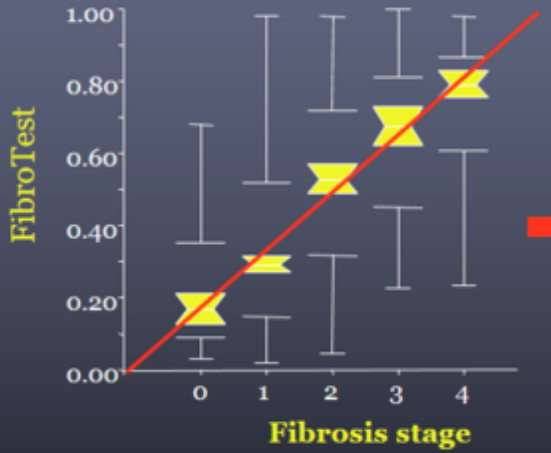
Liver Disease Staging in Decision Making

- 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



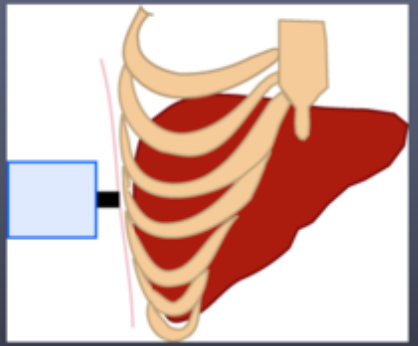
FibroTest	Expected Fibrosis
0.75-1.00	F4
0.73-0.74	F3-F4
0.59-0.72	F3
0.49-0.58	F2
0.32-0.48	F1-F2
0.28-0.31	F1
0.22-0.27	F0-F1
0.00-0.21	F0

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

Poynard T et al. *Clin Chem*. 2004;50:1344-1355.

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