Cirrhosis

1. Are there any cirrhotic patients that we can stop screening for HCC after they are cured of HCV?

HCC and HIV

• Increasing prevalence of HCC with longer life span of HIV
  – Viral hepatitis, ETOH and NAFLD
• Diagnose cirrhosis- Biopsy, Fibroscan, APRI, FIB-4
• Screening for early diagnosis of HCC critical (<30%)
  – all cirrhotics and in HBV non cirrhotics q 6mos
  – Select non cirrhotics F3, HIVuc, older, ?MS
• HIV patients worse outcome ?biology ?screening
• Screening allows access to therapies including locoregional therapy and liver transplant
• Treating viral hepatitis -decreases cirrhosis and HCC
  – Fibroscan appears to underestimate fibrosis stage post SVR
  – HCC can occur after SVR ??higher post DAA
  – Don’t discharge your SVRs from your practice!!!!!!!
Predictors of HCC post HCV SVR- IFN

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR (CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>1.80 (1.2-2.9)</td>
<td>0.005</td>
</tr>
<tr>
<td>Hispanic vs Cauc</td>
<td>2.3 (1.1-4.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Cirrhosis at SVR</td>
<td>6.69 (4.3-10.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1.68 (1.08-2.60)</td>
<td>0.02</td>
</tr>
<tr>
<td>Age 55-64 y</td>
<td>2.04 (1.3-3.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Age &gt;65</td>
<td>4.51 (2.0-10.4)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

El-Serag Hepatology 2016

NASH questions

2. How should we diagnose NAFLD & NASH in our patients (imaging and when to biopsy)
3. Who should we treat?
4. With what?

Diagnosis of Non-Alcoholic Fatty Liver Disease

Abdominal imaging with steatosis (+/- elevated liver enzymes)

Other causes of CLD excluded

Usually with clinical evidence of metabolic syndrome

Steatosis detection - Imaging

• Ultrasound
  – 60–94% sensitivity and 84–95% specificity need >30% fat
• Controlled Attenuation Parameter (CAP) with fibroscan
  – AOC 0.90-0.95 depending on amount steatosis
  – >300 severe (>65%) >?220 moderate
• CT scan
  – Accurate but not sensitive for mild/moderate steatosis
• MRI and MR spectroscopy
  – Can detect small quantity of fat
  – Not in routine use, time consuming

Liver Int. 32, 902–910 (2012)
Radiology 280, 95–102 (2009)
NAFLD: When to Consider a Liver Biopsy?

- Cannot exclude other types of liver disease (autoimmune hepatitis, drug-induced liver disease)
- Atypical phenotype: NAFLD in absence of obesity or metabolic syndrome
- Evidence of iron overload
- Confirm clinical suspicion of cirrhosis
  - Platelet count, imaging, NAFLD fibrosis score
- NASH diagnosis prior to pharmacotherapy
- Support major therapeutic decision - bariatric surgery, clinical trials?

US HIV cohort and steatosis

- 339 HIV subjects London UK
- Hepatic steatosis in 71 (21%) correlated with
  - Abnormal fasting glucose OR 5.5 (5.4, 18.3) p<.001
  - ART NRTI (ddI, d4T, ddC, ZDV) OR 20.34 (1.4, 361.1) p= 0.04
  - Statin therapy OR 3.31 (1.8, 6.2) p<0.001
- Obesity and metabolic syndrome seen in HIV

Mok et al Abstract HIV Drug therapy Glasgow 2016

NASH: Current Standard of Therapy

- First line:
  - Lifestyle modification - weight loss 5-10% through diet and exercise is effective, but high probability of failure
  - Drug therapy of Metabolic syndrome complications - dyslipidemia, hypertension, diabetes

- Second line: Pharmacotherapy for NASH
  - vitamin E for confirmed NASH non DM
  - Obeticholic acid
  - Ineffective or uncertain benefit in NASH: Metformin, UCDA, omega-3 fatty acids, pentoxifylline

- Clinical Trials
  - GFT505, LOXL2

Pioglitazone, Vitamin E, or Placebo for NAS score Improvement in NASH*  

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Placebo</th>
<th>Pioglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Improved</td>
<td>% Improved</td>
<td>% Improved</td>
</tr>
<tr>
<td>Vit E</td>
<td>43%</td>
<td>19%</td>
</tr>
<tr>
<td>Placebo</td>
<td>19%</td>
<td>19%</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>34%</td>
<td>34%</td>
</tr>
</tbody>
</table>

*Decrease in NAS by ≥2 pts with ≥1 point decrease in ballooning.

Sanyal et al, NEJM 2010

No effect on fibrosis

Sanyal et al, NEJM 2010

Pioglitazone in NASH

• Side effect profile may limit use
  – CV events, CHF, weight gain 3-5kg in 70% pts, bladder cancer?, bone fractures in post menopausal women
• Longterm safety and efficacy in NASH unknown

Aliment Pharmacol Ther. 2012

Obeticholic acid (OCA) = potent activator of farnesoid X nuclear receptor in NASH

N=283 72 w

Cenicriviroc: Key Efficacy and Safety Findings

<table>
<thead>
<tr>
<th>Outcome at Yr 1, n (%)</th>
<th>Cenicriviroc (n = 145)</th>
<th>Placebo (n = 144)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in NAS by ≥ 2 points* and no fibrosis worsening</td>
<td>23 (16)</td>
<td>27 (19)</td>
<td>.519</td>
</tr>
<tr>
<td>Complete NASH resolution and no fibrosis worsening</td>
<td>11 (8)</td>
<td>8 (6)</td>
<td>.494</td>
</tr>
<tr>
<td>Improvement in fibrosis stage of ≥ 1 and no NASH worsening</td>
<td>29 (20)</td>
<td>15 (10)</td>
<td>.023</td>
</tr>
<tr>
<td>Grade 3/4 AE</td>
<td>38 (26)*</td>
<td>37 (26)</td>
<td>NR</td>
</tr>
<tr>
<td>Serious AE</td>
<td>16 (11)*</td>
<td>10 (7)</td>
<td>NR</td>
</tr>
</tbody>
</table>

*With ≥ 1 point reduction in lobular inflammation or hepatocellular ballooning.
†Primary endpoint.
*Cenicriviroc safety population, n = 144.


NAFLD Summary

• NAFLD is most common cause of CLD-75-100M individuals in the U.S
• NASH will soon be the leading cause of cirrhosis, HCC, and need for LT
• #1 cause of death in NAFLD is CAD
• Aggressive management of cardiovascular risk factors is essential
• Steatosis is diagnosed by imaging, though diagnosis of NASH requires biopsy
• Common in HIV patients not just NRTI use
  – Associated with metabolic syndrome

Slide credit: clinicaloptions.com
Transplant questions

5. When should HIV/HCV+ patients who are liver transplant candidates be treated for HCV? Before transplant or after?

Spectrum of Cirrhosis Among Patients on the Waiting List

- Compensated cirrhosis
- Child-Pugh A
- MELD <10
- HCC as indication for LT

- Decompensated cirrhosis
- Child-Pugh C
- Severe/refractory portal hypertensive complications
- Moderate-severe liver synthetic dysfunction

Many DAA options
- Higher chance of SVR
- High chance of clinical benefits
- Cure before death likely

Fewer DAA options
- Fewer DAA options
- Slight reduction in SVR
- Risk of dying before or with SVR
- Modest clinical benefits in short-term

Clinical and Biochemical Responses in DAA Treated Patients on Waiting List (CPT A-C)

- French multicenter cohort study
- Complete response: Tbil <1.2, PT<1.2, albumin>3.5 + no ascites or HE
- Partial response: change in CP class
- No response

Rate of Complete Response

- 36% Child A
- 36% Child B
- 28% Child C

Mean follow-up: 68 wks (12-95)

SOF-VEL ± RBV for G1-6 Patients with Child-Pugh B Cirrhosis

- ASTRAL-4
- HCV GT 1-6 patients with CPT B cirrhosis

RBV should be included in treatment of all patients with decompensated cirrhosis, especially G3
SVR is Associated with Clinical and Biochemical Improvements

- 247 patients with decompensated cirrhosis who achieved SVR12
- CPT score change from baseline to 24 Weeks post-Cure in CPT B/C patients

<table>
<thead>
<tr>
<th>CPT Score Change</th>
<th>Improved</th>
<th>No Change</th>
<th>Worsened</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>103</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>67</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>12</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>-1</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>-2</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>-3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- CPT Class improved in 40% (72/180) CPT B patients
- CPT Class improved in 76% (51/67) CPT C patients
  - 64% (43/67) improved to CPT B; 12% (8/67) improved to CPT A

Clinical Outcome in Wait-Listed Patients with CP-B/C Cirrhosis Achieving SVR

- 103 patients listed for decompensated HCV in 11 centers
- Treated with SOF/RBV, SOF/LDV, SOF/DCV, median f/u 52 wks
- 34 deactivated for improvement → 19 formally delisted

Safety of DAA Therapy in Patients with Decompensated Cirrhosis

- Overall, DAAas appear to be safe with relatively low discontinuation rates
- Ribavirin-associated anemia is common and more problematic to manage
- Other AEs consistent with clinical sequelae of advanced liver disease: difficult to determine if DAAs increases risk as most studies are uncontrolled
  - In few controlled studies, AEs predicted by severity of liver disease and not treatment per se
- Lactic acidosis occurred in 5/35 (14%) patients during therapy, while no event of lactic acidosis was observed prior to therapy

To Treat or Not To Treat pre LT?

**No!**
- Lower SVR rates - may end up to DAA resistance → more difficult to treat post-LT
- Few treatment option if develops renal dysfunction
- Likelihood of ending up in MELD purgatory is greater

**Yes!**
- Majority will have improvement in MELD, CPT and symptoms of decompensation
- Modest chance of avoiding liver transplant
- Reduces likelihood of dying before LT
- If transplanted, prevents HCV post-LT
Summary
UCSF Approach with HCV Patients

- Compensated cirrhosis
  - Child-Pugh A
  - MELD <10
- Decompensated cirrhosis (MELD=20)
  - Child-Pugh B
  - Less severe portal HT
- Decompensated cirrhosis (Child-Pugh C)
  - MELD > 20
  - Significant renal dysfunction

- Treat all unless HCC (concern of inability to get to LT with exception status)
- Treat most patients
  - Consider age, severity of PHT complications, severity of necroinflammation
- Don’t treat unless LT is not an option and expected to survive at least 6 months

HCC and HCV: To Treat or Not To Treat?

Yes!
- High chance of cure with 12 weeks therapy
- Keep liver function stable for locoregional therapy
- Prevent worsening decompensation
- Eliminates the risk of HCV post-LT
  - Simplifies management

No!
- Easy to treat post-LT (what’s the rush)
- May have negative impact on HCC- Bad tumor biology
- Needs all options for LT available including anti-HCV+ donors

Risk of HCC Recurrence after Initial Successful Treatment in DAA-Treated Patients

<table>
<thead>
<tr>
<th>Author, Country</th>
<th>N with HCC</th>
<th>N treated with DAA and Timing</th>
<th>Severity of Cirrhosis/HCC</th>
<th>HCC Treatment Given</th>
<th>HCC Recurrence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conti, Italy</td>
<td>59</td>
<td>59 (100%) within Milan</td>
<td>CP A/B</td>
<td>Resection, RFA, TACE, alcohol injection</td>
<td>39% 38 weeks post-DAA therapy</td>
</tr>
<tr>
<td>Reig, Spain</td>
<td>58</td>
<td>58 (100%) within Milan</td>
<td>CP A/B</td>
<td>Resection, ablation, TACE</td>
<td>28% Median 1.5 max after DAA therapy</td>
</tr>
<tr>
<td>Pol, France</td>
<td>79</td>
<td>13 (16%) within Milan</td>
<td>CP A</td>
<td>Resection, ablation or both</td>
<td>1.73 (no DAA) vs 1.11 (DAA) per 100 p-yrs Median time to recur 16.3 months</td>
</tr>
</tbody>
</table>

Whether DAA curative therapy increases risk of HCC recurrence remains a controversial issue

Transplant questions

6. What should our HIV/HCV+ patients who are RENAL transplant candidates be treated? Before or after renal transplant?
Management of HCV in KT Recipients

- HCV-infected KT recipients have higher risk of
  - Overall and liver-related mortality
  - Recurrent HCV-associated renal disease
- Prior strategy for prevention of complications was HCV eradication pre-KT
  - IFN monotherapy was treatment of choice
  - Not all patients eligible and response rates modest
- Changed with
  - DAA regimens
  - HCV positive donors

Severe Renal Impairment CrCl <30 mL/min or End-Stage Renal disease on dialysis

HCV treatment before kidney transplant
- genotype 1a, or 1b, or 4, daily FDC elbasvir (50 mg)/grazoprevir (100mg) for 12 weeks Class IIa, Level B
- genotype 1b daily FDC paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 w Rating: Class IIb, Level B
- HCV genotype 2, 3, 5, or 6 infection PEG-IFN and dose-adjusted ribavirin** (200 mg daily) Rating: Class IIb, Level B
  - ribavirin should be restricted to those with a baseline hemoglobin concentration above 10 g/dL.

AASLD IDSA guidelines 2016

Treatment: pre-KT vs Post-KT

- Even when treatment in dialysis patients is feasible, post-KT may be preferred
  - Maintain ability to receive HCV+ donor kidneys → reduce wait-time by years and waitlist mortality
- Pre-KT treatment may be preferred in patients with advanced liver fibrosis
  - Decrease liver disease progression/need for combined liver/kidney transplant
  - Reduce risk of peri-transplant and early post-transplant liver-related complications
- KT recipients in whom treatment should be prioritized:
  - Recurrent HCV-associated GN and graft dysfunction
  - Progressive or advanced liver fibrosis

HBV questions

7. Can TAF be used in HBV/HIV coinfected patients? Are there any HBV/HIV pts in whom you would NOT use TAF for HBV control?

- Tenofovir (disoproxil fumarate or alafenamide) should be used in all HBV HIV coinfected subjects
- TAF if renal or bone disease, older
  - No data about Fanconi’s recurrence or resolution
HBV questions

8. Why are HBV coinfect patients at risk for reactivation during/after HCV treatment?

HBV Reactivation in Pts Receiving DAAs: Postmarketing Cases Reported to FDA

- Case reports of HBV reactivation in pts receiving DAAs
  - Reactivation: increase in HBV DNA or seroconversion to HBsAg positive
  - 29 confirmed cases in ~3 yrs (November 2013 to October 2016)
    - Pts from Japan (n = 19 ASV), US (n = 5), other (n = 5)
    - Most cases occurred within 4-8 wks of initiation
    - 2 deaths, 1 transplant, 6 hospitalizations, 10 DAA discontinuations

HBV Reactivation Risk in HBV/HCV Coinfected Pts Receiving HCV DAAs

- Case reports of HBV reactivation in pts treated with SMV + SOF ± RBV,[1,2] DCCV + ASV,[3,4] and LDV/SOF[5]
- Observational study of Chinese pts treated with DAAs (N = 327 screened)[6]
  - 3/10 HBsAg+ pts experienced hepatitis due to HBV reactivation
  - Of 124 HBsAg- /HBcAb+ pts, none experienced hepatitis due to HBV reactivation
- Analysis of open-label phase IIIb trial[7]
  - No evidence of HBV reactivation in HBsAg-/HBcAb+ pts receiving LDV/SOF (n = 103)
- Led FDA to require boxed warning for certain DAAs regarding the risk of HBV reactivation and need for HBV screening/monitoring [8]

HBV Reactivation during DAA Rx for HCV

- Cases were not receiving HBV antiviral treatment
- In 8 cases, when transaminases started to rise, DAA hepatotoxicity was initial diagnosis - DAA discontinued.
  As patients deteriorated or failed to improve, HBV reactivation was considered among the likely diagnosis
- 12 cases eventually received HBV antiviral treatment
- Treatment for HBV was delayed in at least five of the 12 cases, and one patient died.
- With HBV treatment, most patients had improvement in HBV DNA, and other signs and symptoms

HBV questions

8. Why are HBV coinfect patients at risk for reactivation during/after HCV treatment?
   • Clearance of one virus may allow for
     – increased activation of other virus (seen with HCV HBV and HBV HDV coinfections- one predominates)
     – Altered immune control of HCC? HCV specific T cells were removed part of HCC control?
   • Pathogenesis studies required

9. Should we prophylax any of our HBV patients against reactivation during HCV treatment including HIV/HCV and HCV monoinfected patients?
   • Is it sufficient to have anti-HBc+ /HBsAg neg patients on lamivudine/FTC as part of ART when undergoing HCV treatment?
   • Or would TDF/TAF based ART be preferable to suppress HBV?

HBV Testing and Monitoring During HCV DAA Therapy: AASLD/IDSA Guidance

• Test all pts initiating HCV therapy for HBsAg, anti-HBc, and anti-HBs
  – No HBV markers: VACCINATE (this is not new)
  – HBV markers present:
    HbsAg positive: Treat with HBV drug
    HBV DNA detectable: Monitor for reactivation; treat if HBV DNA level meets AASLD HBV guideline criteria
    HBV DNA low or undetectable: HBsAg negative; anti-HBc positive (± anti-HBs)
    *Insufficient data to provide recommendations*

Slide credit: clinicaloptions.com
AASLD/IDSA HCV guidance. September 2016. Graphic created by Ira M. Jacobson, MD.
10. Can we cure HBV?
A very brief overview of the sterilizing cure/functional cure argument and the current drug pipeline

**Types of HBV cure**

**Functional Cure- clinical resolution**
Sustained, off drug:
- No inflammation: ALT and liver biopsy
- HBsAg loss
- Anti-HBs gain

**Complete cure - virological cure**
- All of above plus
- Loss of cccDNA in liver

Is **Chronic inactive state** enough
- No inflammation: normal ALT and liver biopsy
- HBV DNA low or u/d
- HBsAg positive

**HBV Control**

- **Inflammatory**: normalize serum ALT, biopsy
- **Virologic**: decrease HBV DNA
- **Immune**: seroconversion
  - HBeAg to anti-HBe
  - HBsAg to anti-HBs
- **HBV as of 2016 not “cured” but controlled**

**Strategies to Eradicate HBV**

**Virologic approaches**
- Entry inhibitors
- Block cccDNA
- Transcription inhibitors
- RNA interference
- HBV capsid inhibitor
- Polymerase inhibitors
- Secretion inhibitors

**Host immune approaches**
- Interferons
- TLR-7
- PD-1/ PDL-1
- IL-7
- Therapeutic vaccines
  - Immune complex vaccines
  - Nasal HBV (NASVAC) vaccines
  - DNA vaccines
  - T cell vaccines
  - Adenovirus based vaccines (TG1050)
  - Yeast based vaccines
Viral Life Cycle - “latent or recovered” HBV: functional cure
Immune system considers this “recovered”
BUT cccDNA remains: template for viral replication

Gonzalez 2015 Antimicrobe