Hepatitis B Pre and Post Liver and Renal Transplant

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Overview of Special HBV Populations

- Decompensated cirrhosis
- Immune suppressed
- Chemotherapy
- Immune tolerant
- Pregnant women
  - Liver Transplant
  - Renal Transplant
Pre Liver Transplant Population
Treatment Goals in HBV-Induced End-Stage Liver Disease

- Reduce Rates of Decompensation
- Improve Survival While Awaiting Transplantation
- Eradicate HBV Before Transplantation to Avoid Recurrence Post-Transplant

Compensated Cirrhosis → Decompensated Cirrhosis → Transplantation → Hepatitis B Recurrence

HCC Risk in Caucasian, Chronic HBV Patients Treated With Entecavir or Tenofovir DF

- Multi-country cohort (Greece, Italy, Turkey, Spain, The Netherlands) (n=1231)
  - Chronic HBV with no co-infection, liver transplantation, or HCC
  - Initiated either entecavir (43%) or tenofovir DF (55%)
- HCC 5-year incidence
  - 4.2% at median of 17 months
  - 13.5 new HCC cases/1000 person-years
- Strongest HCC risk factors
  - Decompensated liver disease (HR: 2.78; \( P=0.019 \)), lower platelet count (HR: 0.97; \( P=0.002 \)), older age (HR: 1.05; \( P=0.12 \))
- Asian-based HCC risk scores may not be applicable to Caucasians with chronic HBV

Study 103 and 102: Tenofovir DF and Regression of Histologic Cirrhosis at Week 240

- There was a progressive decrease in patients with cirrhosis at baseline to year 5
- 74% of patients with cirrhosis at baseline treated with tenofovir DF were no longer cirrhotic at year 5

Paired biopsies at baseline and 240 weeks (n=344).
Chronic Hepatitis Cohort Study: HBV Therapy and Incidence of HCC

- Four, large US healthcare systems (n=2671) (1992-2011)
  - EHR data: virologic laboratory confirmation and/or ICD9 codes consistent with chronic, and confirmation of chronic HBV with chart abstraction
- Antiviral therapy initiated ≥1 year before diagnosis of HCC (n=820)
- Time to HCC incidence
  - EHR ICD9 codes confirmed via chart review and/or tumor registry report as primary a primary liver tumor

### Baseline Characteristics

<table>
<thead>
<tr>
<th>Age (%)</th>
<th>Patients (n=2671)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>28</td>
</tr>
<tr>
<td>&gt;40 to &lt;50 years</td>
<td>24</td>
</tr>
<tr>
<td>50 to &lt;60 years</td>
<td>25</td>
</tr>
<tr>
<td>≥60 years</td>
<td>23</td>
</tr>
</tbody>
</table>

| Male (%)   | 56 |
| Asian ethnicity (%) | 49 |
| Charlson/Deyo comorbidity index score (%) | 75/17 |
| ALT status (%) | Abnormal/normal | 28/55 |

<table>
<thead>
<tr>
<th>Antiviral therapy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleos(t)ide</td>
</tr>
<tr>
<td>Interferon</td>
</tr>
<tr>
<td>Both</td>
</tr>
</tbody>
</table>
Chronic Hepatitis Cohort Study: Predictors of HCC

- HBV antiviral therapy was associated with a 50% decreased risk of developing hepatocellular carcinoma with chronic HBV infection
  - Population analyzed consisted of patients across a spectrum of disease severity
  - Corroborate evidence from previous studies that suggest a reduced risk of HCC with suppression of HBV DNA replication
- Need for prospective studies to substantiate these findings

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard Ratio for HCC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiviral therapy (yes versus no)</td>
<td>0.50* (0.35-0.72)</td>
</tr>
<tr>
<td>Age (versus &lt;40 years)</td>
<td></td>
</tr>
<tr>
<td>40 to &lt;50 years</td>
<td>5.51† (1.74-17.42)</td>
</tr>
<tr>
<td>50 to &lt;60 years</td>
<td>5.55* (1.78-17.28)</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>13.77* (4.54-41.76)</td>
</tr>
<tr>
<td>Charlson/Deyo comorbidity index (versus 0)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.38 (0.87-2.19)</td>
</tr>
<tr>
<td>2 or 3</td>
<td>2.15* (1.46-3.16)</td>
</tr>
<tr>
<td>Male (versus female)</td>
<td>1.94* (1.30-2.87)</td>
</tr>
</tbody>
</table>

*P=0.004 and †P<0.001.

Observed Versus Predicted HCC Cases During Long-Term Tenofovir DF Therapy

Non-Cirrhotic at Baseline

Cirrhotic at Baseline

SIR: standard incidence ratios.

*P<0.05 versus predicted HCC cases.

C-TEAM Study: Long-Term Entecavir and Incidence of HCC in Chronic HBV Infection

- Multi-center observational cohort (17 Taiwanese academic centers)
  - HBsAg positive, anti-HCV negative
  - Treatment-naïve, no HCC development in first year
  - HBV DNA >2000 IU/mL
  - Child A cirrhosis (METAVIR F4 or Ishak >5)

- Study arms
  - Entecavir 0.5 mg (2006-2013; n=666)
    - Follow-up: 2.6 years
    - HCC cases: 16
  - Historical controls (1985-1995; n=621)
    - Untreated
    - Follow-up: 8.5 years
    - HCC cases: 141

Secondary outcomes the 1st 3 years
- No difference between the entecavir and historical control arms
  - Esophageal varices/gastric varices, hepatic encephalopathy, spontaneous bacterial peritonitis, liver-related mortality

Limitations of interim analysis
- Follow-up not yet long enough
- Entecavir arm appeared to have less compensated cirrhosis at baseline

Prolonged entecavir therapy possibly reduced HCC development in HBV-related compensated cirrhotic patients
- Longer follow-up is needed to evaluate impact on cirrhotic complications

Korean Cohort: Antiviral Therapy and Survival in HBV-Related Decompensated Cirrhosis

- Multi-center, prospective cohort (2005-2012)
  - Confirmed onset time and mode of HBV-related decompensated cirrhosis (n=707)
  - Antiviral therapy (60%)
    - Lamivudine, entecavir, adefovir, clevudine, telbivudine
  - Primary endpoint
    - Survival from 1st decompensation to liver transplantation or death
- Sustained viral remission with antiviral therapy in patients with HBV-related decompensation leads to improved long-term survival

Survival by Response to Antiviral Therapy


*\( P < 0.001 \) versus untreated and \( P = 0.01 \) versus non-sustained suppression.
Regimens Post Liver Transplant

- HBIg
- NA
- Combination
- Accelerated Double Dose Vaccination
Recurrence Rates Vary by Regimen
HBV Reinfection After Liver Transplantation

• HBV reinfection after liver transplantation
  – Patients at high-risk for reinfection
    • Cirrhosis (HBeAg positive or negative) plus high HBV DNA levels
    • Antiviral resistance prior to transplantation
  – Patients at low-risk for reinfection
    • Fulminant HBV or co-infection with HDV
    • Cirrhotic, HBeAg negative with low serum HBV DNA levels
  – What is the cut-off for high versus low HBV DNA level?
    • >5 or >3 to 4 log$_{10}$ copies/mL

• De novo HBV infection/reactivation following liver transplantation
  – Up to 10% in HBsAg-negative liver recipients
  – Risk higher when donors are HBsAg negative but anti-HBc positive

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Survival After Liver Transplantation in Recipients With HBV and Other Diagnoses

HBV Prophylaxis for Recipients of Hepatitis B Core Antibody-Positive Liver Grafts

- Immunoprophylaxis regimens after liver transplantation
  - Lamivudine with no HBIG (n=6 studies)
  - Lamivudine + HBIG (n=7 studies)
- Prevention of de novo flares in core positive livers
- Adjunct HBIG and lamivudine alone demonstrated similar efficacy

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>Anti-HBc</th>
<th>Lamivudine Alone</th>
<th>Lamivudine + HBIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>0/13</td>
<td>0/7</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>0/25</td>
<td>1/7</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>1/17</td>
<td>3/20</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>1/18</td>
<td>0/76</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Total</strong></td>
<td>2.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.6%</td>
</tr>
</tbody>
</table>

Hong Kong Cohort: Oral Nucleosides Without HBIG After Liver Transplantation

- **Single-center cohort study** (2003-2011)
  - Chronic HBV patients undergoing liver transplantation (n=362)
  - HBeAg-positive ≥6 months at time of liver transplantation
- **Antiviral prophylaxis**
  - 2003-2007: lamivudine 100 mg/day
  - 2007-2011: entecavir 0.5 mg/day
  - Patients with rt204 mutation: combination therapy*
  - All patients: HBIG not used before, during, or after transplantation
- **Patients followed-up at 3 month intervals (or shorter)**
  - Virologic rebound (HBV DNA ≥1 log$_{10}$ IU/mL)

Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>LVD (n=176)</th>
<th>ETV (n=142)</th>
<th>Combination (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51</td>
<td>52</td>
<td>55</td>
</tr>
<tr>
<td>Male (%)</td>
<td>84</td>
<td>85</td>
<td>84</td>
</tr>
<tr>
<td>MELD score</td>
<td>26</td>
<td>28</td>
<td>17 (P=0.002)</td>
</tr>
<tr>
<td>Transplant type (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceased donor</td>
<td>34</td>
<td>44</td>
<td>45</td>
</tr>
<tr>
<td>Living donor</td>
<td>66</td>
<td>56</td>
<td>55</td>
</tr>
<tr>
<td>Pre-transplant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleosides (%)</td>
<td>30</td>
<td>58</td>
<td>98 (P&lt;0.001)</td>
</tr>
<tr>
<td>HBeAg positive (%)</td>
<td>29</td>
<td>25</td>
<td>57 (P&lt;0.001)</td>
</tr>
<tr>
<td>HBV DNA (log$_{10}$ IU/mL)</td>
<td>3.6</td>
<td>2.7</td>
<td>3.0 (P=0.011)</td>
</tr>
<tr>
<td>Donor anti-HBs positive (%)</td>
<td>63</td>
<td>67</td>
<td>74</td>
</tr>
</tbody>
</table>

*Mostly lamivudine + adefovir.
Hong Kong Cohort: Long-Term Survival and Virologic Rebound

- Long-term survival: 83% at 8 years
- Relative risk of virologic rebound after liver transplantation
  - Lamivudine: 15.21 (2.04-113.29)
  - HCC: 7.48 (1.84-30.37)
  - HBV DNA >3 log$_{10}$ IU/mL: 4.17 (1.81-9.62)
- Use of antiviral with high barrier to resistance is recommended
- Significance of HBsAg status post-liver transplantation remains to be determined

Study 107: Emtricitabine/Tenofovir DF and HBIG Withdrawal in Post-Orthotopic Liver Transplantation

Ongoing Phase 2 Study

Orthotopic liver transplant for HBV infection
12 weeks of stable prophylaxis therapy (FTC/TDF + HBIG)
HBV DNA and HBsAg negative

Randomization 1:1

Open-Label

Emtricitabine/Tenofovir DF (n=37)

Emtricitabine/Tenofovir DF + HBIG (n=19)

Week 24 48 96

Other eligibility criteria: age 18-75 years; no chronic HBV recurrence after transplant; creatinine clearance >40 mL/min; no prior tenofovir or emtricitabine/tenofovir treatment after treatment; HCV, HIV, and HDV sero-negative

### Study 107: Emtricitabine/Tenofovir DF and HBIG Withdrawal in Post-Orthotopic Liver Transplantation: Week 96 Results

<table>
<thead>
<tr>
<th></th>
<th>Emtricitabine/Tenofovir DF (n=18)</th>
<th>Emtricitabine/Tenofovir DF + HBIG (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA negative (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Remained HBsAg negative (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Evidence of HBV recurrence (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Re-initiation of HBIG (%)</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Resistance to emtricitabine/tenofovir DF (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serous adverse events (%)</td>
<td>17</td>
<td>32</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Glucosuria</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Transaminitis</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

HBV Prophylaxis: Liver Transplantation

• Availability of HBIG and antiviral therapy
  – Outcomes of liver transplantation for end-stage HBV disease are now similar to or better than that for other indications

• Treatment goals
  – Reverse cirrhosis complications and need for transplant (ideal)
  – Suppress HBV DNA to the lowest possible level before transplantation

HBV Prophylaxis in Liver Transplantation: Prevention of HBV Reinfection

• No consensus on the most appropriate initial antiviral therapy in this setting

• High-risk patients
  – Nucleoside-naïve patients: entecavir or tenofovir DF
  – Lamivudine-resistant: adefovir or tenofovir DF + lamivudine
  – Monitor regularly, initiate HBIG at the time of transplant and continue antiviral therapy

• Low-risk patients
  – Pre-transplant: benefit of antiviral therapy not established
  – Post-transplant: continue or initiate antiviral therapy
  – HBIG: role is unclear

Lok AS. 2011UpToDate®.
HBV Prophylaxis in Liver Transplantation: Treatment of HBV Recurrence

• No consensus on the most appropriate initial antiviral therapy in this setting

• Treatment depends on prior prophylactic therapy and presence of drug-resistant mutations
  – No prophylaxis or HBIG
    • Tenofovir DF or entecavir
  – Prior lamivudine (most likely lamivudine resistant)
    • Combination therapy with tenofovir DF

Renal Disease and HBV

• Nephropathies
  – MGN
  – MPGN
  – IgA glomerulopathy
  – Polyarteritis nodosa

• Dialysis

• Renal transplant recipients
## Renal Dose Adjustment for NAs

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Lamivudine</th>
<th>Telbivudine</th>
<th>Adefovir</th>
<th>Entecavir</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50</td>
<td>100 mg/d</td>
<td>600 mg/d</td>
<td>10 mg/d</td>
<td>0.5 mg/d</td>
<td>245 mg/d</td>
</tr>
<tr>
<td>30-49</td>
<td>50 mg/d</td>
<td>600 mg/2nd day</td>
<td>10 mg/2nd day</td>
<td>0.25 mg/d</td>
<td>245 mg/2nd day</td>
</tr>
<tr>
<td>10-29</td>
<td>25 mg/d</td>
<td>600 mg/3rd day</td>
<td>10 mg/3rd day</td>
<td>0.15 mg/d</td>
<td>245 mg/3rd-4th day</td>
</tr>
<tr>
<td>&lt; 5-10 or HD²</td>
<td>10 mg/d</td>
<td>600 mg/3rd-4th day</td>
<td>10 mg/wk</td>
<td>0.5 mg/wk</td>
<td>245 mg/wk³</td>
</tr>
</tbody>
</table>
Pre Renal Transplant Evaluation

• 0-20% prevalence of HBV in HD populations
• HBV DNA
• eAg status
• HDV assessment
• Fibrosis staging
  – Biopsy still the gold standard
  – Elastography and non invasive serum markers with normal imaging and biochemical panels

Prophylaxis Post Transplant

• sAg positive
  – Long term therapy recommended

• cAb positive recipient with or without sAb titers
  – No clear data on risk of reactivation
  – Prophylaxis not routinely given, but can be considered

• cAb positive donor
  – Can monitor or give NA prophylaxis
Post Renal Transplant HBV Therapy

Cholangitas, E, et al. World J Gastroenterol 2015
Summary

• Hepatitis B in renal and liver transplant population can be safely and effectively managed

• Renal function should be monitored, esp with nucleotide analogs

• Long term monitoring of HBV DNA and liver chemistries suggested
Conclusion

• HBV in the pre transplant setting must be treated to full suppression if possible
• Recurrence in active infection post transplant can be achieved with NA alone, but perhaps short course HBIG in high risk patients
• Donor positive organs into negative recipients should generally be prophylaxed if close monitoring not feasible