Pre- and Post- Transplantation Management of HBV Patients

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Hepatitis B and Liver Transplant (LT)

- Decline in LT for hepatitis B
- Treatment of patients with HBV-related liver failure
  - Acute liver failure
  - Severe exacerbations of chronic hepatitis B
  - Decompensated cirrhosis
- Prevention of recurrent hepatitis B post-LT
- Treatment of recurrent hepatitis B post-LT
Decrease in Number of HBV Patients Listed for Liver Transplant for ESLD in the U.S. but Increase in Number Listed for HCC

ESLD: endstage liver disease

Approval of lamivudine

ESLD

HCC

ALF

Kim WR, Gastroenterol 2009; 137: 1680
Decrease in Serum HBV DNA after 1 Year of Treatment

LAM = lamivudine, ADV = adefovir, ETV = entecavir, TBV = telbivudine, TDF = tenofovir, PEG-IFN = peginterferon

Not head-to-head comparison, results from various trials combined.
Randomized Controlled Trial of Lamivudine in Severe Acute Hepatitis B

Subacute liver failure
Mean bilirubin 240 umol/L and INR 1.5
Liver transplant not available

3-month mortality

Lamivudine (n=40)
<1 week (n=23)
>1 week (n=17)
Control (n=40)

P=0.03

Yu JW, Dig Dis Sci 2010; 55: 775
Lamivudine Treatment for HBV Acute on Chronic Liver Failure
3-month Mortality without Transplant

9 patients who had liver transplant were excluded

Sun LJ, J Gastroenterol & Hepatol 2010; 25: 583
Entecavir vs. Lamivudine for Severe Acute Exacerbation

36 patients received ETV compared to 117 historical controls that received lamivudine.
Criteria: ALT >10x ULN, Bil >3x ULN.
Tenofovir Improves Survival in HBV-Acute on Chronic Liver Failure

3-month mortality
Tenofovir: 43%
Placebo: 85%

Small no. of patients
Liver transplantation not available

Garg H, Hepatology 2011; 53: 774
Lamivudine Treatment of Decompensated HBV Cirrhosis

Estimated actuarial 3 year survival of patients who survived ≥6 months 88% 

25/32 deaths within first 6 months

N = 154

Patients with less advanced liver failure had improved survival

Fontana RJ, Gastroenterol 2002; 123: 719
Randomized Trial of Entecavir vs. Adefovir in Patients with Decompensated Hepatitis B

<table>
<thead>
<tr>
<th></th>
<th>Week 24</th>
<th></th>
<th>Week 48</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ETV</td>
<td>ADV</td>
<td>ETV</td>
<td>ADV</td>
</tr>
<tr>
<td>% HBV DNA &lt;300 c/mL</td>
<td>49</td>
<td>16</td>
<td>57</td>
<td>20</td>
</tr>
<tr>
<td>% ALT normalization</td>
<td>59</td>
<td>39</td>
<td>63</td>
<td>46</td>
</tr>
<tr>
<td>Mean change in MELD score</td>
<td>-2.0</td>
<td>-0.9</td>
<td>-2.6</td>
<td>-1.7</td>
</tr>
<tr>
<td>% CTP score decrease ≥2 points</td>
<td>32</td>
<td>24</td>
<td>35</td>
<td>27</td>
</tr>
</tbody>
</table>

Cr increase by 0.5 mg/dL by week 96: ETV 17%, ADV 24%
Genotypic resistance: at week 48 - none in both groups, after week 48, 3 ETV-R and 6 ADV-R

Liaw YF, Hepatology 2011; 54: 91
# Tenofvir +/- Emtricitabine vs. Entecavir in Decompensated Hepatitis B – Week 48 Response

<table>
<thead>
<tr>
<th></th>
<th>Tenofvir n=45</th>
<th>Emtricitabine + Tenofovir n=45</th>
<th>Entecavir n=22</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA &lt;400 c/mL</td>
<td>31/44 (71)</td>
<td>36/41 (88)</td>
<td>16/22 (73)</td>
</tr>
<tr>
<td>Decrease in CTP ≥2 point</td>
<td>7/27 (46)</td>
<td>12/25 (48)</td>
<td>5/12 (42)</td>
</tr>
<tr>
<td>Median change in MELD score</td>
<td>5.7</td>
<td>6.3</td>
<td>5.9</td>
</tr>
<tr>
<td>Confirmed increase in Cr &gt;0.5 mg/dL</td>
<td>4 (8.9)</td>
<td>1 (2.2)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Confirmed phosphorus &lt;2.0 mg/dL</td>
<td>1 (2.2)</td>
<td>2 (4.4)</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>2 (4.4)</td>
<td>2 (4.4)</td>
<td>2 (9.1)</td>
</tr>
</tbody>
</table>

Liaw YF, Hepatology 2011; 53: 62
# Nucleos(t)ide Analogues in Decompensated Cirrhosis

<table>
<thead>
<tr>
<th>Antiviral</th>
<th>Fontana</th>
<th>Schiff</th>
<th>Shim</th>
<th>Liaw</th>
<th>Liaw</th>
<th>Chan</th>
<th>Hyun</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs used</td>
<td>LAM</td>
<td>ADV</td>
<td>ETV</td>
<td>ETV/ADV</td>
<td>TDF/FTC + TDF/ETV</td>
<td>TBV/LAM</td>
<td>ETV/LAM</td>
</tr>
<tr>
<td>HBV DNA undetectable, %</td>
<td>&gt;80*</td>
<td>59</td>
<td>89</td>
<td>57/20</td>
<td>71/88/73</td>
<td>65/61</td>
<td>76/47</td>
</tr>
<tr>
<td>ALT normalization, %</td>
<td>NA</td>
<td>77</td>
<td>76</td>
<td>63/46</td>
<td>46/64/41</td>
<td>65/68</td>
<td>NA</td>
</tr>
<tr>
<td>↓CTP score ≥2, %</td>
<td>NA</td>
<td>NA</td>
<td>49</td>
<td>35/27</td>
<td>26/48/42</td>
<td>32/39</td>
<td>NA</td>
</tr>
<tr>
<td>MELD score ↓</td>
<td>NA</td>
<td>-2.0</td>
<td>-2.2</td>
<td>-2.6/-1.7</td>
<td>-2/-2/-2</td>
<td>-1/-2</td>
<td>-4.9/-3.7</td>
</tr>
<tr>
<td>1 year survival, %</td>
<td>84</td>
<td>86</td>
<td>87</td>
<td>77/67</td>
<td>96/96/91</td>
<td>94/88</td>
<td>91/92</td>
</tr>
<tr>
<td>VB or resistance</td>
<td>27</td>
<td>2</td>
<td>0</td>
<td>3/7</td>
<td>0/0/0</td>
<td>27/36</td>
<td>0/17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety</th>
<th>LAM-R flare</th>
<th>Renal 6%</th>
<th>NA</th>
<th>Renal 17%/24%</th>
<th>Renal 9%/7%/5%</th>
<th>Myopathy 1%/0%</th>
<th>NA</th>
</tr>
</thead>
</table>

LAM: lamivudine, ADV: adefovir, ETV: entecavir, TDF: tenofovir, FTC: emtricitabine, TBV: telbivudine

VB = virologic breakthrough

When to Start Antiviral Therapy?

- **As soon as possible** after diagnosis of
  - Hepatitis B (HBsAg, IgM anti-HBc, or HBV DNA positive) and
  - Acute liver failure, or
  - Severe acute hepatitis B or
  - Severe exacerbation of chronic hepatitis, or
  - Decompensated cirrhosis

- **Rationale**
  - Potential for benefit, particularly with early treatment
  - Adverse events rare
  - Reduce risk of HBV recurrence if transplant is needed
Which Antiviral?

- Interferon contraindicated
- Which nucleos/tide analogue (NUC)?
  - Consider antiviral activity, barrier to resistance and prior exposure to NUC
  - First line:
    - NUC-naïve: Entecavir or tenofovir, dose adjust according to renal function
    - NUC-experienced: Tenofovir
    - Combo not superior to monotherapy
Randomized Trial of TDF + FTC vs. TDF in Patients with Lamivudine-resistant HBV

- 280 patients randomized
- At baseline, LAM-R in 99%, ADV-R in 2% and ETV-R in 8-10%
- At week 96, HBV DNA <29 IU/mL in 84% (TDF+FTC) and 86% (TDF), responses similar regardless of ADV exposure and ETV-R

ADV: adefovir, ETV: entecavir, FTC: emtricitabine, LAM: lamivudine, TDF: tenofovir; R=resistance

Fung SK, Gastroenterol 2014; 146: 980
Adverse Effects of Nucleos/tide Analogues

Entecavir - lactic acidosis

- Reported in 5/16 patients in 1 case series\(^1\), associated with MELD ≥20
- Class effect of NUCs / specific for entecavir / other causes such as sepsis?
- Not observed (not systematically monitored) in 2 prospective randomized trials\(^2,3\)

Adefovir and tenofovir – nephrotoxicity

- Confirmed increase in Cr >0.5 mg/dL in 6% patients on transplant waiting list, 47% transplanted during study, and 21% post-transplant patients in 1 study of 467 patients receiving adefovir\(^4\)
- Drug induced / hepatorenal / concomitant nephrotoxic drugs
- No difference in Cr increase compared to entecavir up to 48 weeks\(^2,3\)

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\(^1\)Lange C, Hepatology 2009; 50: 2001  
\(^2\)Liaw YF, Hepatology 2011; 53: 62;  
\(^3\)Liaw YF, Hepatology 2011; 54: 91  
\(^4\)Schiff E, Liver Transpl 2007; 13: 349
Prevention of HBV Recurrence after LT

Evolution of HBV prophylaxis

- Late 1980: ~80% recurrence, LT x HBV not approved by Medicare
- Early 1990: IV HBIG monotherapy
- Late 1990: LAM +/- IV HBIG
- Early 2000: LAM +/- ADV rescue + IV/IM HBIG
- Late 2000: ETV + limited HBIG
- 2016: ETV or TDF alone for low risk patients, ETV or TDF + short duration of HBIG for high risk patients
Risk of HBV Reinfection after LT in Relation to Post-LT HBV Prophylaxis

Entecavir Monotherapy to Prevent HBV Recurrence Post-LT

- 80 patients
- At transplant
  - 22 HBeAg+
  - Median HBV DNA 3.5 (1.5-8.8) log10 c/mL
  - 22 decompensation, 38 acute on chronic flare, 20 HCC
- Median FU 26 (5-40) months
- Pre-LT: 47 antiviral (19 LAM, 28 ETV)
- Post-LT: All continued ETV, none had HBIG
- Cumulative rate of HBsAg clearance at 2 year 91%
- Cumulative rate of HBsAg relapse at 2 year 13.7%
  - 18 patients (22.5%) HBsAg+ at last FU, 16 HBsAg <1 IU/mL
- Only 1 HBV DNA+ (217 c/mL)

Fung J, Gastroenterol 2011; 141: 1212
Entecavir Monotherapy to Prevent HBV Recurrence Post-LT

Fung J, Gastroenterol 2011; 141: 1212
Prevention of Recurrent Hepatitis B after Liver Transplant with Oral Antiviral Alone

362 patients: 176 LAM, 142 ETV. 44 combo (predominantly LAM+ADV)
Median FU 53 months

Liver Histology in LT Recipients Maintained on Oral Antiviral Only

• At time of biopsy
  – 36 HBsAg+, HBV DNA- and 98 HBsAg-
  – None HBsAg+ on immunostaining
  – None had HBV-graft hepatitis
  – For patients without viral rebound, positive HBsAg was not associated with histologic evidence of HBV-related hepatitis

Fung J, Liver Transpl 2015; 21: 1504
Prevention of Recurrent Hepatitis B after Liver Transplant with Oral Antiviral Only

- Feasible in majority of patients if serum HBV DNA at LT low or undetectable, and potent antiviral with high barrier to resistance used
- HBV-hepatitis in graft prevented but not HBV infection
- Higher rate of HBsAg loss than in non-LT setting likely related to removal of infected liver
- High rate of success in studies from endemic areas may be partly related to high prevalence of HBV immunity in donors (passive transfer of donor lymphocytes with transient detection of anti-HBs in recipients)
Algorithm for Prevention of Recurrent Hepatitis B Post-LT

Start NUC: ETV/TDF ASAP
Monitor HBV DNA

Assess risk status at LT

High risk:
- HBV DNA detectable
- HBV antiviral drug resistance
- HIV/HDV coinfection
- HCC

Low risk
- HBV DNA undetectable

- ETV or TDF
- No HBIG

- ETV or TDF
- HBIG: IV peri-transplant, then IM, then stop?
Transplantation of HBsAg-, anti-HBc+ livers into HBsAg- Recipients

• HBV recurrence rate
  – In the absence of HBV prophylaxis
    • Recipient anti-HBs+ and/or anti-HBc+: 0-20%
    • Recipient anti-HBs- and anti-HBc-: 50-95%
  – With HBV prophylaxis
    • HBIG monotherapy: 0-100%
    • HBIG + lamivudine: 0-11%
    • Lamivudine only: 0% (0/19 patients)

Takemura N Dig Dis Sci 2007; 52: 2472
Algorithm for Use of Liver Grafts from Anti-HBc+ Donors in HBsAg- Recipients

- Consensus guidelines by a panel of experts
- Endorsed by American Society of Transplantation and Canadian Society of Transplantation

Huprikar S, Am J Transplant 2015; 15: 1162
Algorithm for Use of Liver Grafts from Anti-HBc+ Donors in HBsAg- Recipients

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**Diagram:**

- **Anti-HBc+ HBsAg– Donor**
  - anti-HBc+ anti-HBs+ Recipient
    - Consider no prophylaxis
  - anti-HBc– anti-HBs+ Recipient
    - Lamivudine
  - anti-HBc– anti-HBs– Recipient
    - Lamivudine

**Medications:**

- ETV/TDF Booster HBV vaccine
- ETV/TDF Booster HBV vaccine
- ETV/TDF

Management of Recurrent Hepatitis B

• **Definition**
  - HBV reinfection - detection of HBsAg or serum HBV DNA, or
  - HBV hepatitis – biochemical/histological

• Should be <1% in properly managed patients who are compliant

• Graft loss and mortality can be prevented if diagnosed early

• Most (>90%) cases due to antiviral +/- HBIG resistance mutations

• Rescue therapy tailored according to suspected drug resistance, genotypic resistance testing whenever possible especially in patients exposed to >1 nucleos/tide analogue

• HBIG should be stopped
### Rescue Therapy Options for Antiviral Drug-resistance HBV

<table>
<thead>
<tr>
<th>Type of resistance</th>
<th>Preferred rescue therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine or Telbivudine</td>
<td>• Switch to tenofovir</td>
</tr>
<tr>
<td></td>
<td>• Add tenofovir or switch to Truvada</td>
</tr>
<tr>
<td>Adefovir</td>
<td>• Switch to entecavir (if no prior LAM-R) or tenofovir</td>
</tr>
<tr>
<td></td>
<td>• Switch to Truvada</td>
</tr>
<tr>
<td>Entecavir</td>
<td>• Switch to tenofovir</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>• Switch to entecavir</td>
</tr>
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</table>