Safety of Nucleos(t)ide Analogues during Long-Term Treatment of Chronic Hepatitis B

Anna S. F. Lok, MD
Alice Lohrman Andrews Research Professor in Hepatology
Director of Clinical Hepatology
University of Michigan
Ann Arbor, MI, USA
Approved HBV Treatments

- Interferon alpha 2b (Intron)
- Pegylated interferon alpha 2a (Pegasys)
- Lamivudine (Epivir)
- Adefovir (Hepsera)
- Entecavir (Baraclude)
- Telbivudine (Tyzeka)
- Tenofovir (Viread)

Treatments approved for HIV with activity against HBV
- Emtricitabine (Emtriva)
- Tenofovir + Emtricitabine (Truvada)
Safety of NUCs during Long-Term Treatment of CHB

• Loss of efficacy / Drug resistance
• Adverse events
HBV DNA Suppression During Continued Treatment with NUC in HBeAg+ Patients

Not head to head comparison, different HBV DNA assays used
LAM = lamivudine, ADV = adefovir, ETV = entecavir, TBV = telbivudine, TDF = tenofovir
Virologic Response to Entecavir in an Italian Cohort Real-Life Study

Compared to phase III trial, patients were older, 90% genotype D, 49% cirrhosis
No resistance documented

Lampertico P, AASLD 2011, abs 1436
Virologic Response to Tenofovir in the European Cohort Real-Life Study

% of patients with undetectable HBV DNA

Lampertico P, AASLD 2011; abs 1433
Resistance to Nucleos(t)ide Analogues

- Virologic breakthrough
  - >1 log increase in serum HBV DNA from nadir during treatment or redetection of HBV DNA after being undetectable

- Confirmed virologic breakthrough
  - Confirmation of virologic breakthrough on repeat test

- Genotypic resistance
  - Detection of mutations documented to decrease susceptibility to the antiviral drug
Patients with HBV DNA ≥400 copies/mL at Week 72 could add FTC to TDF; * Cumulative probabilities of resistance taken; † Naïve HBeAg (+); ‡ Naïve HBeAg(-); N/A not available.

High Rate of Entecavir Resistance in Lamivudine-Refractory HBeAg+ Patients

ETVr = LVDr (M204V ± L180M) + T184, S202 and/or M250 substitutions
ETVr + Virologic Breakthrough (≥1 log increase from nadir)

- 72/187 (39%) achieved HBV DNA < 300 cp/mL;
- 3/72 (4%) had subsequent genotypic ETV resistance

Tenney D, Hepatology 2009; 49: 1503
# Virologic Breakthrough and Genotypic Resistance to NUCs

## Phase III Clinical Trials – End of Year 1

<table>
<thead>
<tr>
<th></th>
<th>Virologic breakthrough (VBT)</th>
<th>Genotypic resistance (GR)</th>
<th>% VBT not attributable to drug resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>13.8%</td>
<td>10.3%</td>
<td>25.4%</td>
</tr>
<tr>
<td>Adefovir</td>
<td>8.2%</td>
<td>0.8%</td>
<td>90.2%</td>
</tr>
<tr>
<td>Entecavir</td>
<td>1.6%</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>4.7%</td>
<td>4.1%</td>
<td>12.8%</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>2.3%</td>
<td>0%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Genotypic Changes in HBV Polymerase During Year 5 of Tenofovir Treatment

Patients on TDF Monotherapy (n=6)  Patients on FTC+TDF Therapy (n=6)

- 12/495 patients had HBV DNA >400 copies/mL during year 5
- One subject on FTC/TDF developed a rtK168N conserved site change (non-adherent)
- Five subjects developed polymorphic site changes and all were unique
- None of the changes decrease susceptibility to TDF

Marcellin P, AASLD 2011; abs 238
HBV DNA Profile for a Patient with Incomplete Viral Suppression on TDF and Virologic Breakthrough on FTC/TDF

Patient A (Genotype C)

Marcellin P, AASLD 2011; abs 238
Adherence to HBV Nucleos(t)ide Analogue Therapy in Clinical Practice

- Phase III clinical trials:
  - 13%-100% of patients with VBT not associated with emergence of drug resistance mutations
  - Medication nonadherence may be responsible for VBT in these patients

- Adherence in clinical practice likely lower
  - Patients less motivated, more comorbid conditions
  - Monitoring less frequent
  - Patients often have to pay for medications in part or in full
Persistence of HBV Nucleos(t)ide Analogues

- Pharmacy refill rates declined sharply in first 6 months, particularly among patients newly started on treatment.
- Pharmacy refill persisted until the end of the year in
  - 73% of new patients
  - 81% of existing patients

Chotiyaputta W, J Hepatol 2011; 54: 12
Adherence to HBV Nucleos(t)ide Analogs:
Analysis of pharmacy claims database in 3 cohorts of patients treated in the US in 2007, 2008 and 2009

Adherence (％ of days in that year in which patients have medications in their hands)
<80％ in ~20％ patients
How to Maintain Viral Suppression?

- Use most potent drugs that have highest genetic barrier to resistance
- Counsel patients on importance of medication adherence at the start and regularly throughout the course of treatment
- Monitor virologic response closely
- Confirm virologic breakthrough +/- test for antiviral drug resistance mutation before modifying treatment
Safety of NUCs during Long-Term Treatment of CHB

- Loss of efficacy / Drug resistance
- Adverse events
  - ARA-AMP peripheral neuropathy
  - FIAU lactic acidosis, liver failure, and death
  - Clevudine mitochondrial toxicity, myopathy and neuropathy
  - AEs emerged during later phase trials or after approval when drugs were used for longer duration
Adverse Effects of HBV Nucleos(t)ide Analogues – Year 1

• Phase III placebo-controlled trials
  – Lamivudine vs. placebo
  – Adefovir vs. placebo - higher frequency of confirmed increase in creatinine in adefovir 30 mg dose group

• Phase III / IV active control trials
  – Entecavir vs. lamivudine or adefovir*
  – Telbivudine vs. lamivudine or adefovir *
  – Tenofovir vs. adefovir*

Similar frequency of adverse events

*Adefovir 10 mg
Adverse Effects of HBV Nucleos(t)ide Analogues

• Lactic acidosis, mitochondrial toxicity
• Entecavir – lactic acidosis
• Adefovir and tenofovir – nephrotoxicity
• Tenofovir – decrease bone mineral density
• Telbivudine – myopathy, peripheral neuropathy
Safety of 3 year Telbivudine Treatment in Patients with CHB

- 399 patients
- AE leading to treatment discontinuation: 2 (0.5%)
- New onset grade 3/4 CK elevations: 55 (13.3%)
- Myalgia: 22 (5.3%), 5 felt to be treatment-related
- Myositis: 2 (0.5%)
- Muscle weakness: 2 (0.5%)
- Peripheral neuropathy: 0

Gane E, Liver Int 2011; 31: 676
Long-Term Safety of Adefovir Phase III Trials: 4-5 year Treatment

• HBeAg+ patients (n=65)
  – 6 confirmed increase in Cr by >0.5 mg/dL
  – 2 confirmed phosphorus <2.0 mg/dL

• HBeAg- patients (n=125)
  – 4 confirmed increase in Cr by >0.5 mg/dL
  – No confirmed hypophosphatemia

Renal Tubular dysfunction (RTD) during Long-term Adefovir or Tenofovir Therapy in CHB

- 51 patients treated for 1-10 years (mean 7.4)
- 42 ADV, 4 TDF, 5 ADV followed by TDF
- Estimated 10 yr cumulative rate of 15%
- Risk factors: older age, lower baseline GFR
- 6 patients with RTD switched to entecavir, all had improvement in renal function

Gara N, Aliment Pharmacol Ther 2012; 35: 1317
Long-Term Safety of Entecavir in Patients with Chronic Hepatitis B

1051 patients rolled over from 10 phase II/III studies, median time on entecavir 184 weeks (range 1.9-380)

<table>
<thead>
<tr>
<th>HBeAg</th>
<th>ETV-901 cohort (n=1051)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>41 (17-78)</td>
</tr>
<tr>
<td>Men</td>
<td>77</td>
</tr>
<tr>
<td>Caucasian</td>
<td>46</td>
</tr>
<tr>
<td>Mean ALT, IU/L</td>
<td>111 (6-2067)</td>
</tr>
<tr>
<td>Mean Cr, mg/dL</td>
<td>0.9 (0.5-2.6)</td>
</tr>
<tr>
<td>Time on entecavir</td>
<td></td>
</tr>
<tr>
<td>Median, weeks</td>
<td>184 (1.9-380)</td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td>49%</td>
</tr>
</tbody>
</table>

Manns MP, Expert Opin Drug Saf 2012
Long-Term Safety of Entecavir in Patients with Chronic Hepatitis B

<table>
<thead>
<tr>
<th>Event</th>
<th>ETV-901 cohort (n=1051)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>900 (85.6)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>169 (16.1)</td>
</tr>
<tr>
<td>Discontinuations due to AEs</td>
<td>14 (1.3)</td>
</tr>
<tr>
<td>Grade 3-4 AEs due to entecavir</td>
<td>45 (4.3)</td>
</tr>
<tr>
<td>On-treatment ALT flares</td>
<td>32 (3.0)</td>
</tr>
<tr>
<td>Deaths</td>
<td>27 (2.6)</td>
</tr>
<tr>
<td>Liver-related</td>
<td>12 (1.1)</td>
</tr>
<tr>
<td>Non liver-related</td>
<td>15 (1.4)</td>
</tr>
</tbody>
</table>

Manns MP, Expert Opin Drug Saf 2012
Lactic Acidosis during Entecavir Treatment in Patients with Impaired Liver Function

- Case series - 5/16 patients with cirrhosis developed lactic acidosis (all had MELD score ≥20) 4-240 days after starting ETV, 1 patient died

- 2 randomized trials in patients with decompensated cirrhosis, lactic acidosis not observed
  - ETV (n=22, MELD 11) vs. TDF vs. TDF/FTC
  - ETV (n=100), MELD 17) vs. ADV

Long Term Safety of Tenofovir: Phase III Trials Through 5 Years of Follow-up

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Total no. of patients (n=585)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE leading to study drug discontinuation</td>
<td>8 (1.4%)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>9 (1.5%)</td>
</tr>
<tr>
<td>Grade 3 or 4 AE</td>
<td>7 (1.2%)</td>
</tr>
<tr>
<td>Confirmed serum creatinine ≥ 0.5 mg/dL above Baseline</td>
<td>5 (0.9%)</td>
</tr>
<tr>
<td>Confirmed PO₄ &lt; 2 mg/dL</td>
<td>7 (1.2%)</td>
</tr>
<tr>
<td>Confirmed creatinine clearance &lt; 50 mL/min</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

1 Total number of TDF-treated patients in the open-label phase of HBeAg+ and HBeAg- studies
2 Study drug-related AEs

Marcellin P, AASLD 2011: abs, 238 & 1375
### Association of Tenofovir Exposure with Kidney Disease Risk in HIV Infection

HIV+ VA patients initiated ART 1997-2007
6538 no TDF and 4303 TDF exposure, median followup 3.9-5.5 yrs

<table>
<thead>
<tr>
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<th>HR (per year exposure to TDF)</th>
<th>95% CI</th>
<th>P value</th>
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<tbody>
<tr>
<td>Proteinuria</td>
<td>1.34</td>
<td>1.25-1.45</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rapid decline in GFR</td>
<td>1.11</td>
<td>1.03-1.18</td>
<td>0.0033</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1.33</td>
<td>1.18-1.51</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Proteinuria $\geq 30$ mg/dL
Rapid decline in GFR: annual decline of $\geq 3$ ml/min/1.73m$^2$
Chronic kidney disease: eGFR $<60$ ml/min/1.73m$^2$

*Scherzer R, AIDS 2012; 26: 867*
Safety of HBV NUCs
FDA Black box Warning

- Severe acute exacerbation of chronic hepatitis B have been reported in patients who have discontinued anti-HBV therapy.
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported.
Safety of Tenofovir: FDA Black box Warning

• Renal
  – Renal impairment including acute renal failure and Fanconi syndrome have been reported
  – Serum Cr and PO4 should be monitored
  – Tenofovir should be avoided with concurrent or recent use of a nephrotoxic agent

• Bone
  – Decrease in bone mineral density and increase in biochemical markers of bone turnover have been reported but effects on future fracture risk are unknown
  – Cases of osteomalacia (associated with proximal renal tubulopathy) have been reported
  – Bone effects in HBV monoinfected patients unknown
Which is the Best Initial Nucelos(t)ide Analogue?

**Long-term Benefits**
- Antiviral potency
- Durability of response

**Long-term Risks**
- Ease of administration
- Comorbid conditions
- Costs of Rx & monitoring
- Patient preference (family planning)
- Side effects
- Drug resistance