New perspective of anti-viral therapy in chronic hepatitis B

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What’s New?
Evolving treatment guidelines in Hepatitis B
APASL guideline 2012
Recommendation 5 - Which drug or strategy

- Nucleos(t)ide analogs (NA)-naïve patients can be treated with IFNa (IB), Peg IFN (IA), ETV (IA), TDF (IA), ADV (IB), LdT (IB) or LAM (IB). Thymosin-a can also be used (IB).

- ETV or TDF is the preferred NA
ETV or TDF is the preferred NA
Because of the high antiviral potency, low resistance profile
Drug resistance of different NAs

Low genetic barrier

High genetic barrier

- Lamivudine: Year 1 (24), Year 2 (38), Year 3 (49), Year 4 (67), Year 5 (70)
- Adefovir: Year 2 (3), Year 3 (11), Year 4 (18), Year 5 (29)
- Telbivudine: Year 5 (4), No data
- Entecavir: Year 1 (0.2), Year 2 (1.2), Year 3 (1.2), Year 4 (1.2), Year 5 (up to 6 years)
- Tenofovir: Year 1 (0), Year 2 (0), Year 3 (0), Year 4 (0), Year 5 (0)

Data from AASLD 2012

Ayoub and Keeffe. Aliment Pharmacol Ther 2011
Long-term efficacy of entecavir in trial setting

Proportion of patients with HBV DNA <300 copies/mL, %

Year 1 | Year 1 | Year 2 | Year 3 | Year 4 | Year 5
--- | --- | --- | --- | --- | ---
67% | 55% | 83% | 89% | 91% | 94%
236/354 | 80/146 | 116/140 | 116/131 | 98/108 | 88/94*

* Five patients who remained on treatment at the Year 5 visit had missing PCR values (Non-completer = missing).

Chang TT, et al. Hepatology 2010
Long-term efficacy of entecavir in real-life setting

Week 48 viral load and 3-year outcomes

HBeAg-positive (N = 160)  
HBeAg-negative (N = 280)

Maintained viral suppression at 3 years, %

HBV DNA at week 48 < 20 IU/ml achieved in 324/440 (74%) patients

Entecavir resistance at 3 years, %

Only 1/116 (0.9%) developed drug resistance even HBV DNA at week 48 ≥ 20 IU/ml

Low resistance with entecavir in real-life cohorts


- **ORIENTE study**
  - No resistance has been observed up to 1 year (n = 190)

- **VIRGIL (naïve)**
  - No resistance has been documented up to 3 years (n = 333)

- **Italian cohort**
  - One patient (0.2%) developed ETV resistance over 42 months (n = 418)

- **Hong Kong study**
  - One patient (0.2%) developed ETV resistance in 3 years (n = 440)
Liver fibrosis improved with long-term ETV

Ishak fibrosis score

- Missing
- 6
- 5
- 4
- 3
- 2
- 1
- 0

* Up to 7 years
Range: 3–7 years
Median time: 280 weeks†

† In the randomized controlled studies, patients received 0.5 mg ETV. In the 901 rollover study, patients received 1 mg ETV.

Chang TT, et al. Hepatology 2010
Virologic response during ETV is not influenced by severity of liver disease

Virologic response: HBV DNA <80 IU/mL

Patients with virologic response (%)

Time (weeks)

P = 0.62

No cirrhosis n=274
Cirrhosis n=89
 Decompensated cirrhosis n=9

Virologic response is associated with a lower probability of disease progression.

Remained significant when correcting for age or MELD score.

Hazard rate (HR): 0.29, 95% CI 0.08–1.00

Efficacy of 48 weeks ETV in LAM/LdT-experienced HBeAg(−) patients

Among patients with quantifiable HBV DNA or ALT test results at baseline and Week 48, con-completer = missing.

The majority of patients who achieved HBV <50 IU/ml also achieved HBV DNA <12 IU/mL.

Hou JL, et al. APASL 2011
Efficacy of 48 weeks ETV in ADV-experienced patients

16% of HBeAg(+) patients experienced HBeAg loss; 12% seroconverted

Hou JL, et al. APASL 2011
Long-term efficacy of ETV in ADV-experienced patients

- ETV was analysed for 43 of 51 ADV-experienced (+LAM experienced in 29 [67%]) patients who were directly switched to ETV
- One (2.3%) patient experienced virological breakthrough and developed genotypic ETV resistance

Adjusted estimated survival curve for the cumulative probability of achieving virological response. For ADV-naïve, ADV-experienced patients and ADV-resistant patients. Based on a Cox’s model for mean values of baseline HBV DNA, ALT, HBeAg status and previous LAM exposure and resistance.
Long-term efficacy of tenofovir in trial setting

*Study 102 (HBeAg- Patients) and 103 (HBeAg+ Patients)*

- **Randomization 2:1**
  - Pre-treatment Liver Biopsy
  - **Tenofovir DF 300 mg**
    - **N=250 & N=176**
  - **Adefovir Dipivoxil 10 mg**
    - **N=125 & N=90**

Year 1
- **Liver Biopsy**
- **Year 1 Liver Biopsy**
- **Tenofovir DF 300 mg**
  - **N=235**
  - **N=154**
- **Adefovir Dipivoxil 10 mg**
  - **N=112**
  - **N=84**

Year 3
- **Liver Biopsy**
- **Week 72**
- **Year 5/ Week 240**
- **Liver Biopsy**
- **Year 8**

- **At Week 72**, patients with HBV DNA \( \geq 400 \text{ copies/mL} \) had the option at the discretion of the investigator to add emtricitabine (FTC)

- **Retention rate at Week 240**: 81% for HBeAg-, 70% for HBeAg+
Long-term efficacy of tenofovir in trial setting

**HBeAg-positive patients: On-Treatment**

- TDF-TDF 99%
- ADV-TDF 99%

**HBeAg-negative patients: On-Treatment**

- TDF-TDF 100%
- ADV-TDF 96%

No Resistance to TDF up to 6 years

Marcellin et al. AASLD 2012
Liver fibrosis regression with long-term TDF

- Patients with Ishak score ≤2: 39% at Baseline, 63% at Year 5
- Patients with Ishak score ≥4: 38% at Baseline, 12% at Year 5
- Patients with cirrhosis (Ishak score ≥5): 28% at Baseline, 8% at Year 5

Gane et al. APASL 2012
Regression of cirrhosis with long-term TDF

- 28% (96/348) of patients with paired biopsies had cirrhosis at Baseline
- 74% (71/96) were no longer cirrhotic (Ishak score <5) at Year 5

Change in Ishak Scores at Year 5 for Patients with Cirrhosis at Baseline

73% of patients had ≥2 unit reduction

Gane et al. APASL 2012
Long-term efficacy of TDF in real-life setting
European Retrospective/prospective multicenter cohort study

% patients with undetectable HBV DNA

<table>
<thead>
<tr>
<th>Month</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
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</thead>
<tbody>
<tr>
<td>%</td>
<td>65</td>
<td>84</td>
<td>91</td>
<td>90</td>
<td>91</td>
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</tbody>
</table>

HBeAg seroconversion:
15 patients**

% patients with HBeAg seroconversion

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>61</th>
<th>55</th>
<th>45</th>
<th>32</th>
<th>20</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>0</td>
<td>6</td>
<td>12</td>
<td>18</td>
<td>24</td>
<td>33</td>
</tr>
</tbody>
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Lampertico P, et al. AASLD 2011
Efficacy of TDF in Rx-experienced patients in real-life setting
The “Geminis” German Multicenter Observational Study

N = 400, FU up to 3 years
Results of interim analysis at 1 year

Petersen J, et al. EASL 2012
Combining ETV and TDF?

The BE-LOW study (ETV-110)

Randomized, open-label, Phase IIIb trial
NA-naïve CHB, HBeAg(-) patients capped at 30%

Baseline

ETV 0.5 mg, once daily
(N = 182) *

ETV 0.5 mg + TDF 300 mg, once daily
(N = 197) *

Further anti-HBV therapy at discretion of investigator – up to 24 weeks follow-up

Week 96
Primary endpoint

Combining ETV and TDF?

The BE-LOW study (ETV-110)

ETV + TDF: no overall benefit c.f. ETV mono (low dose)

May benefit in HBeAg(+) with baseline HBV DNA ≥ 10^8 IU/mL

Alternatives: high dose ETV or TDF monotherapy??

Lok, AS, et al. Gastroenterology 2012
How about safety profile of ETV and TDF?
Asian patients are at risks of renal and bone problems because of common comorbidities.
Long-term safety of TDF in real-life setting

- The proportion with GFR <50 mL/min remained stable over targeted renal therapy (~3–4%)
- 11 (4%) patients had a decline in MDRD and required dose reduction or discontinuation

<table>
<thead>
<tr>
<th>Renal function</th>
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<tbody>
<tr>
<td>Baseline creatinine, mg/dL*</td>
<td>0.90 (0.4–5.2)</td>
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<tr>
<td>Year 2 creatinine, mg/dL*</td>
<td>0.90 (0.5–8.2)</td>
</tr>
<tr>
<td>&gt;0.5 mg/dL increase creatinine</td>
<td>~1%</td>
</tr>
<tr>
<td>Low phosphorus (&lt;2.0 mg/dL)</td>
<td>~1%</td>
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<tr>
<td>Proteinuria (30 mg by dip stick)</td>
<td>~1%</td>
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<table>
<thead>
<tr>
<th>Other variables</th>
<th></th>
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<tr>
<td>Dose changes due to AEs‡</td>
<td>9 (3%)</td>
</tr>
<tr>
<td>Drug discontinuations due to AEs§</td>
<td>9 (3%)</td>
</tr>
</tbody>
</table>

Renal related in 4%

Lampertico P, et al. AASLD 2011
Renal function in 160 patients treated with ETV or TDF

Risk factors:
History of organ transplantation – adjusted OR = 6.74
Pre-existing renal insufficiency – adjusted OR = 10.96

Considerations in the prevention of drug-induced renal and bone problems

- Be aware of patient-related risk factors

- General measures to prevent nephrotoxicity
  - Avoid nephrotoxic combinations
  - Adjust medication dosages based on renal function

- Tests to exclude both tubular and glomerular renal toxicity
  - GFR and estimating equations can not detect tubular damage
  - Phosphate wasting, glycosuria, and proteinuria can be detected in patients with proximal tubular dysfunction

Conclusions & Perspective

• ETV or TDF are the preferred NAs in chronic hepatitis B patients.

• High antiviral potency and low risk of drug resistance is confirmed in both trial and real-life settings for ETV and TDF.

• Beware of renal and bone toxicity in long-term users.

• Perspective: more potent viral suppression, better clinical outcomes?