Hepatitis B Virus therapy

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Disclosures

• **Advisor:** AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, Novartis

• **Lecturer:** Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, Novartis

• **Clinical trials:** Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, Novartis, Roche
Natural history of CHB

Chronic hepatitis B infection

Treatment not indicated
- Immune tolerant HBV
- HBV carrier state

Treatment indicated
- Chronic hepatitis
  - ALT elevated
  - HBV DNA >2000 IU/mL
  - Fibrosis
- Cirrhosis
- Decompensated cirrhosis

ALT: alanine aminotransferase; HBV: hepatitis B virus
What can be achieved now

• In immune tolerant patients

• In patients with CHB and cirrhosis

• In decompensated patients

CHB: chronic hepatitis B
Long-term follow-up of immune tolerant patients

- Consecutive immune tolerant patients
  - HBsAg- and HBeAg- for > 6 months
  - Normal ALT levels on 3 consecutive readings over 6 months
  - HBV DNA >10^7 copies/mL
- 57 patients followed up for 5 years
- 84% of patients remained immune tolerant at Year 5
- No HCC


HBsAg: hepatitis B surface antigen; HBeAg: hepatitis B ‘e’ antigen; HCC: hepatocellular carcinoma
What can be achieved now in immune tolerant patients?

TDF and FTC/TDF in patients with normal ALT and high HBV DNA
Phase 2, randomised, double-blind study in HBeAg-positive patients

HBV DNA $\geq 10^8$ copies/mL
ALT $\leq$ ULN
(N=126)

Randomised to TDF for 192 weeks (n=64)
Completed study through Week 192 (n=53; 83%)

Randomised to FTC/TDF for 192 weeks (n=62)
Completed study through Week 192 (n=54; 87%)

Discontinued treatment before Week 192 (n=11; 17%)

Discontinued treatment before Week 192 (n=8; 13%)

FTC/TDF and FTC are investigational agents and not licensed for use in CHB; TDF: tenofovir disoproxil fumarate; FTC: emtricitabine; UNL: upper normal limit

HBV DNA suppression in immune tolerant patients

- 6% TDF patients and 2% TDF/FTC achieved HBeAg loss
- 5% TDF patients and 0% TDF/FTC achieved HBeAg seroconversion
- There were no cases of HBsAg loss/seroconversion
- No patients developed HCC or clinical events

What can be achieved now?

• In immune tolerant patients
• In patients with CHB and cirrhosis
• In decompensated patients
Chronic hepatitis B infection

Treatment not indicated
• Immune tolerant HBV
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Treatment indicated
• Chronic hepatitis
  – ALT elevated
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• Cirrhosis
• Decompensated cirrhosis
### Approved Agents used to Treat HBV

<table>
<thead>
<tr>
<th>Agent</th>
<th>Year(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>1997, 1999</td>
</tr>
<tr>
<td>Entecavir</td>
<td>2002, 2005</td>
</tr>
<tr>
<td>Adefovir</td>
<td>2002, 2005</td>
</tr>
<tr>
<td>Peginterferon alpha-2b</td>
<td>2005</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>2005, 2006</td>
</tr>
<tr>
<td>Interferon alpha-2a</td>
<td>2005, 2006</td>
</tr>
<tr>
<td>Peginterferon alpha-2b</td>
<td>2005</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>2005, 2006</td>
</tr>
</tbody>
</table>
Therapeutic strategies for chronic hepatitis B

Short-term "curative" treatment

- IFN
- On treatment response
- Follow-up (mo/ yrs)
- HBV DNA < 2000 IU/ml
- ALT < UNL (anti-HBe)
- HBsAg Loss

Long-term "suppressive" treatment

- NUC
- HBV DNA undetectable by PCR (<10-15 IU)
- HBsAg loss
Therapeutic Strategies for Chronic Hepatitis B

**NAs**

- Single mode
- Potent antiviral effect

**(PEG)-IFN**

- Dual mode of action
- Immunomodulatory effect and Antiviral effect
Peginterferon alfa-2a versus Lamivudine Alone or in Combination in HBeAg-Positive Patients

HBeAg-POSITIVE Patients: Week 72 Treatment Response

Peginterferon alfa-2a versus Lamivudine Alone or in Combination in HBeAg-Negative Patients

HBeAg-NEGATIVE Patients: Week 72 Treatment Response

Impact of (peg)-IFN therapy on CHB

- Safety profile well known
- Progression to cirrhosis prevented
- Clinical decompensation prevented
- HCC reduced (?)
- Improved patient survival
- Immune control status in 30% of patients
How can we improve PEG-IFN efficacy?

- **pretreatment** predictors of response
  - High ALT levels
  - Low levels HBV DNA
  - Genotype A
  - Young people

- **on-treatment** predictors of response
Response-guided therapy (RGT) using HBsAg levels in Peg-IFN-treated patients: to identify non responders

**HBeAg-positive**

**Week 12:**
- No decline of HBsAg (A,D)
- HBsAg >20,000 IU/mL (B,C)

**Week 24:**
- HBsAg >20,000 IU/ml (A,B,C,D)

**HBeAg-negative (geno D)**

**Week 12:**
- No decline in HBsAg +
  <2 log decline in HBV DNA

* 97-100% Negative Predictive Values

Sonneveld et al. Hepatology 2010
Piratvisuth et al. APASL 2010
Liaw et al. Hepatology 2011
Sonneveld et al., Hepatology 2013
Rijckborst et al. Hepatology 2010
Rijckborst / Lampertico et al. J Hepatol 2012
Response-guided therapy by HBsAg levels in Peg-IFN-treated patients: to identify non responders

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HBeAg-negative (geno D)

Week 12:
- No decline in HBsAg + <2 log decline in HBV DNA

20% of patients can stop Peg-IFN at week 12

* 97-100% Negative Predictive Values

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Therapeutic Strategies for Chronic Hepatitis B

NAs

Single mode
Potent antiviral effect

(PEG)-IFN

Dual mode of action
Immunomodulatory effect and Antiviral effect
# High virological responses with long-term ETV or TDF

<table>
<thead>
<tr>
<th>Response</th>
<th>ETV</th>
<th>TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBeAg+ patients Year 5&lt;sup&gt;1&lt;/sup&gt;</td>
<td>HBeAg-patients Year 3&lt;sup&gt;2, a&lt;/sup&gt;</td>
</tr>
<tr>
<td>HBV DNA suppression&lt;sup&gt;b&lt;/sup&gt;</td>
<td>94% (88/94)</td>
<td>95% (54/57)</td>
</tr>
<tr>
<td>Resistance</td>
<td>1% (n=1)</td>
<td>NR</td>
</tr>
<tr>
<td>HBsAg loss (seroconversion)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

<sup>a</sup>ETV re-treatment (relapsed <6 months post-treatment in ETV-027 study);
<sup>b</sup>TDF: HBV DNA <400 copies/mL, ETV: HBV DNA <300 copies/mL;
ETV: entecavir; NR: not reported

CIBERHEP: Efficacy of TDF in Treatment naïve and Treatment Experienced patients

- Patients (N=370) from 48 Spanish centres treated for 12–295 weeks

- HBsAg loss: n=4 (1 HBsAg seroconversion)

Viral suppression was similar between TN and TE patients, with HBeAg loss occurring more in TN patients

Tabernero D. EASL 2014; Poster 1058

TE: treatment experienced; TN: treatment naïve
VIREAL study: high rates of virological response, regardless of age

- Subgroup (n=48) of elderly patients (≥65 years)

- Incidence of comorbidities in elderly patients:
  - 35% hypertension
  - 17% diabetes
  - 58% F3–F4 (METAVIR) at baseline

TDF has not been studied in patients >65 years. As elderly patients are more likely to have decreased renal function, caution is required in these patients (Viread SmPC, March 2014)
Liver fibrosis regression and cirrhosis reversal over 5 years of treatment with TDF

- N=348 had biopsies at baseline and Year 5 (96 with cirrhosis)

74% (71/96) had reversal of cirrhosis

Δ Ishak Fibrosis Score over 5 years in patients with cirrhosis

Histologically evaluable patients in the long-term histology cohort
Characteristics of patients shown to be associated with reversal of cirrhosis with TDF

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No cirrhosis at Year 5 (n=71)</th>
<th>Cirrhosis at Year 5 (n=25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BMI at baseline, kg/m² (SD)</td>
<td>25.7 (3.7)</td>
<td>29.0 (4.4)</td>
<td>0.0007</td>
</tr>
<tr>
<td>BMI (kg/m²) at baseline, %</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normal (&lt;25)</td>
<td>41</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Overweight (25–&lt;30)</td>
<td>49</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Obese (≥30)</td>
<td>10</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Diabetes at baseline, %</td>
<td>1</td>
<td>24</td>
<td>0.001</td>
</tr>
<tr>
<td>Normal ALT on treatment, %</td>
<td>87</td>
<td>58</td>
<td>0.007</td>
</tr>
</tbody>
</table>

BMI: body mass index; SD: standard deviation

Risk of HCC is predicted to be decreased with long-term therapy

- 7.4-year long-term follow-up from pivotal TDF studies (N=641) compared with predicted rate of HCC from 3 new models
- Risk models predicted similar scores that were consistently higher than the 14 cases of HCC that occurred during follow-up (n=404)
- Despite viral suppression by TDF there is still risk of HCC
  - Need for constant monitoring for HCC


GAG-HCC: Guide with Age, Gender, HBV DNA, Core promoter mutations and Cirrhosis; REACH-B: Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B
Japanese cohorts: significantly reduced HCC incidence with ETV compared with controls in cirrhotic patients


LAM: lamivudine
Lower risk of death/transplantation with ETV than with LAM

**Death or transplantation**

<table>
<thead>
<tr>
<th>Years after starting treatment</th>
<th>Estimated cumulative incidence of death or transplantation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
</tr>
</tbody>
</table>

No. at risk

<table>
<thead>
<tr>
<th>LAM</th>
<th>1792</th>
<th>1778</th>
<th>1740</th>
<th>1660</th>
<th>1601</th>
<th>1531</th>
<th>1389</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETV</td>
<td>1792</td>
<td>1777</td>
<td>1436</td>
<td>966</td>
<td>563</td>
<td>224</td>
<td>21</td>
</tr>
</tbody>
</table>

**HCC**

<table>
<thead>
<tr>
<th>Years after starting treatment</th>
<th>Estimated cumulative incidence of HCC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
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<td>5</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

No. at risk

<table>
<thead>
<tr>
<th>LAM</th>
<th>1792</th>
<th>1777</th>
<th>1699</th>
<th>1585</th>
<th>1496</th>
<th>1409</th>
<th>1262</th>
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</thead>
<tbody>
<tr>
<td>ETV</td>
<td>1792</td>
<td>1777</td>
<td>1384</td>
<td>911</td>
<td>511</td>
<td>200</td>
<td>19</td>
</tr>
</tbody>
</table>

\[ P<0.001 \]

\[ P=0.95 \]

## When to stop NA therapy?

<table>
<thead>
<tr>
<th></th>
<th>EASL 2012 guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg positive</strong></td>
<td>A) Confirmed anti-HBe seroconversion (and undetectable HBV DNA) after at least 12 months of consolidation*</td>
</tr>
<tr>
<td></td>
<td>B) Confirmed HBsAg loss and anti-HBs seroconversion</td>
</tr>
<tr>
<td><strong>HBeAg negative</strong></td>
<td>Confirmed HBsAg loss and anti-HBs seroconversion</td>
</tr>
<tr>
<td><strong>Cirrhotics</strong></td>
<td>Confirmed HBsAg loss and anti-HBs seroconversion</td>
</tr>
</tbody>
</table>

*A proportion of patients who discontinue nucleos(t)ide analogue (NA) therapy after anti-HBe seroconversion may require retreatment, since they fail to sustain their serological and/or virological response; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen.

Adapted from EASL Clinical Practice Guidelines. J Hepatol 2012;57:167–85
Off-therapy durability of response to ETV in HBeAg-negative CHB from Taiwan

• 95 patients (39 cirrhotic) treated with ETV for 24 (13–59) months
• Stopping rule: undetectable HBV DNA on 3 occasions at least 6 months apart
• Response after treatment discontinuation compared with LAM or LdT from historical data
• Cumulative relapse rates in Year 1:
  – Virological relapse: 58%
  – Clinical relapse: 45%
• No good predictors of relapse

qHBsAg predicts HBsAg loss and HBV relapse after LAM discontinuation in HBeAg -ve


*Defined as serum HBV DNA >2,000 IU/mL in 2 measurements at least 3 months apart
Stopping TDF After Long-Term Virologic Suppression in HBeAg-Negative CHB

FINITE CHB, a randomized study in non cirrhotic HBeAg-ve patients with 4 yrs TDF therapy and undetectable HBV DNA

Randomized N=45

Withdrew consent n=3

TDF-Stop n=21

Week 48
TDF-Restart n=3

Week 48
TDF-Stop n=18

Week 48
TDF-Continue n=21

86% of TDF-Stop subjects did not restart TDF by Week 48

Berg, EASL, 2015, O119
FINITE CHB study 48 weeks outcome after therapy discontinuation

TDF-Stop: HBsAg loss, HBV DNA, ALT, TDF-Restart

![Bar chart showing outcomes at Week 12, Week 24, and Week 48](image-url)
FINITE CHB. HBsAg levels between Patients who TDF stopped and those who TDF continued

**Week 48 HBsAg log\(_{10}\) Reduction (Individual Patients)**

Stopping TDF was associated with a more profound decline in HBsAg levels compared to continuous TDF.

**Berg, EASL, 2015, O119**
HBsAg Clearance After Addition of PegIFN for 48 Weeks in HBeAg-Negative CHB Patients on NUCs

**ANRS-HB06 PEGAN Study**

Multicenter, randomized, controlled study in 183 patients with documented undetectable HBV DNA while on NUCs for at least 1 year

<table>
<thead>
<tr>
<th>NUC alone (n=93)</th>
<th>NUC + PegIFN (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 0</td>
<td></td>
</tr>
<tr>
<td>Wk 48</td>
<td></td>
</tr>
<tr>
<td>Wk 96</td>
<td></td>
</tr>
<tr>
<td>Wk 144</td>
<td></td>
</tr>
</tbody>
</table>

| HBsAg loss (Week 48, %) | 0 (0) | 7 (8) | 0.0057 |
| HBsAg loss (Week 96, %) | 3 (3) | 7 (8) | 0.1521 |
| HBs seroconversion (Week 96, %) | 1 (1) | 6 (7) | 0.0465 |

Patients receiving add-on PegIFN experienced higher HBsAg loss than NUC monotherapy at W48, but without statistical difference at W96
HBsAg loss with TDF plus PEG in chronic hepatitis B (CHB): Results of a global randomized controlled trial at week 72

Start TDF during follow-up if prespecified safety criteria met

- HBsAg Loss:
  - TDF + PEG: 9%
  - TDF+PEG → TDF: 2.8%
  - TDF: 0%
  - PEG: 2.8%

- HBeAg Loss:
  - 29%
  - 25%
  - 15%
  - 25%

¾ from Asian
No cirrhosis and bridging fibrosis were excluded

Marcellin P, et al. AASLD 2014
### Baseline and On-Treatment Predictors of HBsAg Loss at Week 72

<table>
<thead>
<tr>
<th></th>
<th>Baseline Predictors</th>
<th>On-Treatment Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Predictors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype A vs B</td>
<td>0.024</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Genotype A vs C</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Genotype A vs D</td>
<td>0.004</td>
<td>0.007</td>
</tr>
<tr>
<td>Arm A vs B</td>
<td>0.030</td>
<td>0.017</td>
</tr>
<tr>
<td>Arm A vs C</td>
<td>0.018</td>
<td>0.070</td>
</tr>
<tr>
<td>Arm A vs D</td>
<td>0.031</td>
<td>0.014</td>
</tr>
</tbody>
</table>

### Treatment Groups
- **Arm A**: PegIFN+TDF x 48 weeks
- **Arm B**: PegIFN+TDF x 16 weeks, TDF x 32 weeks
- **Arm C**: TDF x 120 weeks
- **Arm D**: pegIFN x 48 weeks

*Chan, EASL, 2015, O117*
High negative predictive values are seen among patients treated with TDF + PegIFN combination if they have:

- HBsAg decline < 1 log_{10} IU/mL at Week 12
What can be achieved now?

- High rates of virological response with low/no risk of resistance
- Histological improvement
- Stop progression of disease (decompensation) and reduced liver transplant
- Reduced risk of HCC