Optimal therapy of CHB: how do I treat my HBeAg negative patients?

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Financial Disclosures

► Advisory Board/Speaker Bureau for:

BMS, ROCHE, GILEAD, MSD, GSK
Outline

► Peg-IFN
► How to improve PEG-IFN response
► Third generation NUC (ETV and TDF)
► Stopping rules for NUC
► Combination therapy (Peg-IFN+NUC)
Peg-IFN
Treatment aims to enable patients to achieve inactive CHB with sustained immune control.

Approximately 30% of patients respond to treatment with Peg-IFN alfa-2a.

Peg-IFN alfa-2a treatment can also result in off-treatment immune control.

Potential long-term clinical benefits of sustained immune control after a finite course of Peg-IFN alfa-2a therapy:

- Freedom from potentially life-long treatment
- No long-term safety concerns
- Decreased risk of cirrhosis and liver cancer
- HBsAg clearance (clinical cure)

References:
The S-Collate study (European cohort) sustained responses in HBeAg negative patients

- **HBV DNA <2000 IU/mL**
  - Week 48 (EOT): 91%
  - 6 months of FU: 65%
  - 12 months of FU: 70%

- **HBsAg clearance**
  - Week 48 (EOT): 6%
  - 6 months of FU: 7%
  - 12 months of FU: 8%

Marcellin P et al, AASLD 2013 (A 939)
Extending PEG-IFN in HBeAg-negative disease reduces relapse: PegBeLiver study

96% genotype D

N=51
PEGASYS 180 Follow-up

N=52
PEGASYS 180 PEGASYS 135 Follow-up

Study weeks

0 48 96 114

HBV DNA <2000 IU/mL

29%

HBsAg clearance

0%

Duration of therapy (weeks)

48 96

12%

48 96

6%

Extending therapy can increase response rate in genotype D patients

Lampertico et al. GUT 2013
Baseline predictors of response: accurate prediction of response allows more informed treatment decisions

### Baseline factors associated with sustained response in patients receiving Peg-IFN alfa-2a

**HBeAg-positive patients**
- Low HBsAg
- High ALT (2 × ULN)
- Low viral load (HBV DNA <2 × 10^8 IU/mL)
- **HBV genotype** (A > B > C > D)
- **Female** gender
- **Wild-type** vs precore/core promoter mutations

**HBeAg-negative patients**

Similar to those observed in HBeAg-positive patients but less well defined

Other biomarkers (including IP10) are under investigation; data from recent studies investigating the relationship between IL28B and response have been controversial and are currently under discussion.

7. de Niet A, et al. EASL 2013

IL28B = interleukin 28B
IP10 = interferon gamma-inducible protein-10
ULN = upper limit of normal
### PEG-IFN for HBeAg negative CHB

**Scoring system for predictive baseline characteristics (4 variables)**

- 263 patients included (Roche registration trials and PegBeliver)
- Age 41, 79% male, 61% Asian, 24% B, 35% C, 32% D, qHBsAg 3.4 log, DNA 6.4 log
- Predictive baseline characteristics for each individual patient were assigned points, which were summed
- A score ranging from 0 to 6, with higher scores indicating a higher chance of SIC and SR, was generated

<table>
<thead>
<tr>
<th>BASELINE CHARACTERISTICS</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV genotype: Non-CC</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Age, years: &gt;45</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>≥30–≤45</td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
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<tr>
<td>HBsAg, IU/mL: ≥3500</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>≥1000–&lt;3500</td>
</tr>
<tr>
<td></td>
<td>&lt;1000</td>
</tr>
<tr>
<td>ALT ratio, x ULN: &lt;5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>≥5</td>
</tr>
</tbody>
</table>

Lampertico P et al, AASLD 2014
PEG-IFN for HBeAg negative CHB
Baseline predictive score

<table>
<thead>
<tr>
<th>Baseline Predictive score</th>
<th>Patients (%)</th>
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<tbody>
<tr>
<td>0–1 (39%)</td>
<td>n: 12, N: 9</td>
</tr>
<tr>
<td>2–3 (49%)</td>
<td>n: 29, N: 24</td>
</tr>
<tr>
<td>≥4 (13%)</td>
<td>n: 61, N: 79</td>
</tr>
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Lampertico P et al, AASLD 2014
Response-guided therapy (RGT) using HBsAg levels in HBeAg negative Peg-IFN-treated patients

**Responders**

Week 12 - 24 (geno D):
- ≥10% decline HBsAg

47-57% Positive Predictive Values

**Non responders**

Week 12 (geno D):
- No decline in HBsAg + <2 log decline in HBV DNA

97-100% Negative Predictive Values

Marcellin et al, APASL 2010
Lampertico et al. EASL 2012

Rijckborst et al. Hepatology 2010
Rijckborst / Lampertico et al. J Hepatol 2012
Response-guided therapy (RGT) using HBsAg levels in HBeAg negative Peg-IFN-treated patients

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

* 47-57% Positive Predictive Values

* 97-100% Negative Predictive Values

Marcellin et al, APASL 2010
Lampertico et al. EASL 2012
Rijckborst et al. Hepatology 2010
Rijckborst / Lampertico et al. J Hepatol 2012
The importance of HBsAg quantification and on-treatment monitoring

- Quantification of HBsAg levels is an accepted clinical tool to determine response to treatment
  - regular monitoring is recommended by both EASL and NICE guidelines
  - integral to the stopping rules for Peg-IFN
- HBsAg seroconversion is considered the optimal goal of antiviral treatment
  - indicates resolution of chronic HBV infection

qHBsAg

2. Hepatitis B (chronic): Clinical guideline (June 2013) available at:

qHBsAg = quantitative HBsAg
5 years ETV for real life, naive CHB patients
Virological summary

Europe1 97%  n=744
Italy2 99%  n=418
Hong-Kong3 97%  n=222
Japan4 100%  n=252
China5 100%  n=117
Thailand6 96%  n=535

3-4 years TDF for real life, naive CHB patients

Virological summary

<table>
<thead>
<tr>
<th>Country</th>
<th>Years</th>
<th>Percentage</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany1</td>
<td>3 yrs</td>
<td>92%</td>
<td>184</td>
</tr>
<tr>
<td>France2</td>
<td>3 yrs</td>
<td>94%</td>
<td>440</td>
</tr>
<tr>
<td>Spain4</td>
<td>4 yrs</td>
<td>100%</td>
<td>180</td>
</tr>
<tr>
<td>Europe4</td>
<td>4 yrs</td>
<td>97%</td>
<td>374</td>
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## 8 years TDF for naïve CHB patients

### Efficacy summary

<table>
<thead>
<tr>
<th>%</th>
<th>HBeAg- n=375</th>
<th>HBeAg+ n=266</th>
</tr>
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<tbody>
<tr>
<td><strong>HBV DNA</strong></td>
<td>ITT1</td>
<td>Observed2</td>
</tr>
<tr>
<td>&lt;69 IU/mL</td>
<td>75</td>
<td>99.6</td>
</tr>
<tr>
<td>&lt;29 IU/mL</td>
<td>74</td>
<td>99</td>
</tr>
<tr>
<td><strong>HBeAg loss / seroconvert.</strong></td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>HBsAg loss / seroconversion</strong></td>
<td>1.1 / 0.7</td>
<td>1.1 / 0.7</td>
</tr>
</tbody>
</table>

1 Missing/addition of FTC = failure [LTE-TDF]; 2 Missing=excluded/addition of FTC = included.; 3 Kaplan-Meier (KM-ITT); NA = not applicable

No resistance to TDF detected

Marcellin P et al, AASLD 2014
## Management of HBV Resistance (Early rescue)

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<th>Resistance</th>
<th>Recommendation</th>
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<tr>
<td>LAM resistance</td>
<td>Switch to TDF (or add ADV)</td>
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<tr>
<td>LDT resistance</td>
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<tr>
<td>ETV resistance</td>
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| ADV resistance | Switch to ETV or TDF (LAM naive)  
Switch to ETV (LAM naive + HVL)  
Switch to TDF and add a nucleoside (LAM resist.) |
| TDF resistance** | Switch to ETV (LAM naive)  
Add ETV (LAM resistant)* |

*the long-term safety of these combinations is unknown  
**not seen so far; do genotyping and phenotyping in an expert lab to determine the cross-resistance profile

adapted from EASL HBV guidelines, J Hepatol 2012
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>95% viral suppression by early add-on ADV or TDF monotherapy

adapted from EASL HBV guidelines, J Hepatol 2012
5-7 years of ETV or TDF therapy for CHB

- Viral suppression in >95% naïve/NUC-R patients
- HBsAg clearance in 1%
- ALT normalization in ~85%
- No major safety issues
- Fibrosis regression in 80% of chronic hepatitis patients and in 75% cirrhotics
- Clinical decompensation prevented, portal hypertension improved
- HCC rates unchanged/reduced (?)
When to stop NUC therapy?
### When to stop NUC therapy?

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

* A proportion of patients who discontinue NUC therapy after anti-HBe seroconversion may require retreatment, since they fail to sustain their serological and/or virological response

adapted from EASL HBV Guidelines, J Hepatol 2012  
Reijnders JG and Janssen HL. Hepatology 2013  
Lampertico P. Gut 2014
qHBsAg predicts HBsAg loss and HBV relapse after LAM discontinuation among HBeAg negative patients from Taiwan (105 patients)

*defined as serum HBV DNA >2,000 IU/mL in 2 measurements at least 3 months apart

Chen CH et al, J Hepatol 2014
De-novo PEG + NUC combination in naive CHB patients

(to improve PEG)
PEG vs PEG+TDF vs TDF - Study Design

Randomized, controlled, open-label study (N=740)
- Stratified by screening HBeAg status and HBV genotype

Inclusion criteria
- HBeAg+ and HBV DNA ≥20,000 IU/mL; HBeAg- and HBV DNA ≥2,000 IU/mL
- ALT >54 and ≤400 U/L (men); ALT >36 and ≤300 U/L (women)
- No bridging fibrosis or cirrhosis on liver biopsy or by transient elastography

Start TDF during follow-up if pre-specified safety criteria met

Marcellin P et al, AASLD 2014
**HBsAg Decline by HBeAg Status and Treatment Arm at week 48**

<table>
<thead>
<tr>
<th>HBeAg status</th>
<th>TDF + PEG 48 wk n=186</th>
<th>TDF + PEG 16 wk →TDF 32 wk n=184</th>
<th>TDF 120 wk n=185</th>
<th>PEG 48 wk n=185</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>-1.3</td>
<td>-0.8</td>
<td>-0.5</td>
<td>-0.9</td>
</tr>
<tr>
<td>Negative</td>
<td>-0.9</td>
<td>-0.2</td>
<td>0.0</td>
<td>-0.6</td>
</tr>
</tbody>
</table>

Mean change in qHBsAg (log IU/ml) from baseline to wk 48

~50% higher qHBsAg decline in PEG+TDF vs PEG

Marcellin P et al, AASLD 2014
HBsAg Loss by Genotype at Week 72* in HBeAg negative patients

Number of patients with HBsAg loss

A*
- TDF + PEG 48 Wk: N=78, 1 (7.7%), 1 (1.2%), 3 (4.0%) for Genotypes A, B, C, D
- TDF + PEG→TDF: N=80, 0 (0.0%), 3 (3.7%) for Genotypes A, B
- TDF: N=75, 1 (1.3%) for Genotype A
- PEG: N=77, 0 (0.0%), 1 (1.3%) for Genotype A

B**
- TDF + PEG 48 Wk: N=78, 0 (0.0%), 6 (7.7%) for Genotypes A, B
- TDF + PEG→TDF: N=80, 1 (1.2%) for Genotype B
- TDF: N=75, 0 (0.0%), 1 (1.3%) for Genotype A
- PEG: N=77, 0 (0.0%), 1 (1.3%) for Genotype A

* Missing = failure analysis
** Raw numbers analysis

Adapted from Marcellin P et al, AASLD 2014
PEG + NUC combination in NUC responders

(to improve NUC)
A RCT of 48 wk add-on Peg-IFN in HBeAg neg, NUC responders - PEGAN study

(183 patients, age 48, 86% male, 40% Caucasians, qHBsAg 3520 IU/ml, 100% PCR neg, 85% on ETV/TDF)

Primary analysis* (ITT)

NUC: 1% (1/93) HBsAg loss 8.0% (7/90)
NUC+PEG: 1% (1/93) HBsAg loss 8.0% (7/85)

Secondary analysis* (mITT)

NUC: 1% (1/91) HBsAg loss 9.0% (7/82)

* p<0.05

Bourliere M. et al, AASLD 2014
48 week Add-on Peg-IFN in HBeAg neg, geno D, NUC responders - HERMES study
(70 patients - Week 24 interim analysis)

Patients:
50 yr, 81% male, 100% Caucasian, 100% geno D, 100% with HBV-DNA negative and normal ALT levels
Undetectable HBV DNA for 3.2 years (1.1-8) before add-on PEG

Lampertico P. et al, AASLD 2014
Conclusions (I)

✓ **Short-term PEG-IFN therapy:**
  - 48-week course effective in 20-30% of patients
  - Baseline prediction score developed (4 variables)
  - qHBsAg at week 12 as a stopping rule (97-100% NPV)
  - Cost-effectiveness must be improved (new rules)

✓ **Long-term NUC therapy:**
  - Long-term ETV or TDF monotherapy for most patients
  - Very effective (>90%), no major safety signals over 5 years
  - Decompensation prevented, HCC reduced (?)
  - New stopping rules needed (qHBsAg ?)

✓ **Candidates for therapy:**
  - Cirrhosis: all HBsAg and HBV DNA pos (any level)
  - Chronic hepatitis: HBsAg + DNA + ALT + liver disease
**Conclusions (II)**

✓ **Combination therapy (PEG + NUC):**
  - De-novo combo in naïve pts; add-on in NUC responders
  - Higher qHBsAg decline
  - Greater HBsAg loss (4-5 times more)
  - Caveats: few patients respond → prediction rules (PPV)
  - Caveats: higher costs, more side effects
  - Not ready for clinical practice yet