Hepatitis B: is there still a role for interferon?

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PHC 2018 – www.aphc.info
Disclosures

Advisory Board/Speaker Bureau for:

- BMS, ROCHE, GILEAD SCIENCES, GSK, ABBVIE, MSD, ARROWHEAD, ALNYLAM, JANSSEN
Outline of the presentation

- Peg-IFN for NUC naïve patients
  - Pre- and on-treatment predictors
- Peg-IFN for NUC treated patients
  - De novo combination
  - Switch to or add-on strategies
- New HBV biomarkers
Peg-IFN for NUC-naive patients
What can we achieve with Peg-IFN alfa-2a in CHB?

- Treatment aims to enable patients to achieve inactive CHB with sustained immune control.

Approximately 20-30% 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:
Baseline prediction score for Asian HBeAg positive CHB
A multicenter retrospective study

647 HBeAg-positive patients from China, Hong Kong and Taiwan

Five baseline factors:
age, gender, ALT, qHBsAg, HBV DNA

Chan H et al, submitted 2017
Baseline prediction scores for HBeAg negative CHB
A multicenter retrospective study

323 HBeAg negative CHB patients treated with Peg-IFN alfa 2a

Four baseline variables:
age, ALT, HBV genotype, qHBsAg

Three baseline variables:
age, qHBsAg, HBV DNA

Lampertico P et al, submitted 2018
Genetic variation in STAT4 predicts response to IFN-alpha therapy for HBeAg positive Chinese CHB

466 HBeAg-positive CHB patients treated with IFNa-2b or peg-IFNa-2a therapy for 48 weeks

Multivariate Analysis:
STAT 4 rs7574865 (GG genotype): OR 0.34, 95%CI 0.21-0.55, p<0.0001
Gender (female): OR 2.09, 95%CI 1.25-3.49, p=0.01
Baseline ALT (>120 IU/L): OR 1.80, 95%CI 1.00-3.23, p=0.05

Jiang DK et al, Hepatology 2016;63:1102-1111
IFNL4 rs368234815 and rs117648444 variants predict off-treatment HBsAg loss in IFN-treated HBeAg-neg CHB

126 HBeAg-negative CHB patients treated with IFN and followed for 11 (1-23) years

Multivariate analysis: HBV DNA levels, log10 IU/mL HR 0.57, 95%CI 0.39 - 0.83, p=0.003; No IFNλ4 + IFNλ4-S70a: HR 5.90, 95%CI 1.70 - 21), p=0.006

Galmozzi E et al, Liver International 2017
Genetic Variation in *FCER1A* Predicts Peg-IFN Alfa-2a-Induced HBsAg Clearance in East Asian Patients With CHB

- GWAS study in 1,636 treated with IFN alpha 2a
- In gene-by-gene analysis, one gene, *FCER1A* (rs7549785), reached genome-wide significance ($P = 2.65 \times 10^{-8}$) in East Asian patients for HBsAg loss. *FCER1A* encodes the alpha subunit of the immunoglobulin E receptor.

- In a post hoc analysis of a homogenous patient subset, the strongest intra-genic association was for *rs7712322 (POLR3G*, $P = 7.21 \times 10^{-7}$). *POLR3G* encodes the G subunit of the Polymerase (RNA) III enzyme, which plays a key role in sensing and limiting infection by intracellular bacteria and DNA viruses, and acts as nuclear and cytosolic DNA sensor involved in innate immune response.

*Wei L et al, Submitted 2018*
GWAS study in 1045 IFN treated CHB patients
NCOA2 Region on Chr. 8 in Caucasians

Identified an interesting region on chromosome 8 (NCOA2)
- P-value of lead SNP in Caucasians is $1.3 \times 10^{-6}$; MAF=0.13
- Not associated in Asians (p=0.557)
- Nuclear hormone receptor involved in activation of cell cycle genes

**NCOA2 is:**
- A modulator of hepatic metabolism (Chopra et al., 2011)
- Implicated as a tumour suppressor in liver cancer of mice (O’Donnell et al., 2012)
- Known to be associated with spindle cell rhabdomyosarcoma and an oncogene in prostate cancer (Troutman 2010)
- Associated with hs-cardiac tropin T-levels (Yu et al., 2013)
Week 12 and 24 stopping rules for HBeAg-positive and -negative patients treated with PegIFNa

**Week 12**
- Stop if HBsAg

**Week 24**
- Stop if HBsAg

### HBeAg-positive CHB

- **Genotype**
  - A: No decline
  - B: >20,000
  - C: >20,000
  - D: No decline

### HBeAg-negative CHB (genotype D)

- **HBsAg levels**
  - Any decline
  - No decline

- **HBV DNA levels**
  - >2 log decline
  - <2 log decline

**EASL 2017 HBV guidelines, J Hepatol 2017**
Peg-IFN alfa-2a (40KD) treatment stopping rules in CHB: A systematic review and individual patient data meta-analysis

1,423 patients (765 HBeAg-positive; 658 HBeAg-negative) from 8 studies were included.

### Performance characteristics of proposed Week 12 stopping rules

<table>
<thead>
<tr>
<th>HBV Genotype</th>
<th>Stopping rule</th>
<th>Se</th>
<th>Sp</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg-positive patients</strong></td>
<td></td>
<td></td>
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<tr>
<td>B</td>
<td>HBsAg &gt;20,000 IU/mL</td>
<td>0.96</td>
<td>0.23</td>
<td>0.93</td>
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<td>HBV DNA &gt;8 log(_{10}) IU/mL</td>
<td>0.94</td>
<td>0.26</td>
<td>0.90</td>
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<td>HBV DNA &gt;8 log(_{10}) IU/mL</td>
<td>0.98</td>
<td>0.19</td>
<td>0.98</td>
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<td><strong>HBeAg-negative patients</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>D</td>
<td>HBsAg &gt;20,000 IU/mL</td>
<td>0.94</td>
<td>0.16</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>HBV DNA &gt;6.5 log(_{10}) IU/mL</td>
<td>1.00</td>
<td>0.11</td>
<td>1.00</td>
</tr>
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Se, sensitivity; Sp, specificity; NPV, negative predictive value; HBeAg, hepatitis B ‘e’ antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

- These early stopping rules have been externally validated in the same paper.
- The performance of Week 24 stopping rules was similar.
- For HBeAg negative geno D patients, the PARC rule at week 12 performed as well.

Pavlovic V et al, submitted 2018
Peg-IFN for NUC-treated patients
PEG-IFN and NUC – Combination strategies aimed to achieve HBsAg decline or loss

- De-novo combination (naïve pts)
- “Switch” NUC to PEG
- “Add-on” PEG to NUC
7 patients had HBsAg seroreversion on or after Week 48 (4 in TDF+PEG 48 wk, 3 in TDF+PEG 16 wk →TDF 32 wk)

- 5/7 had ≤1 week of therapy after HBsAg loss
"Switch to" PEG long-term ETV treated pts
Results at week 48* - mITT

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<td>HBeAg loss</td>
<td>16 (38%)</td>
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<td>14 (15%)</td>
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<td>4 (4.4%)</td>
<td>&lt;0.0001</td>
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<td>HBsAg &lt;10 IU/ml</td>
<td>13 (16%)</td>
<td>0</td>
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<td>HBsAg loss</td>
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<td>48 (58%)</td>
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*End of treatment for PEG

Ning Q, et al, J Hepatol 2014
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Ning Q, et al, J Hepatol 2014
The New Switch study
“Switch to” PEG-IFN for NUC treated HBeAg pos pts
Serological response rates at week 48

Week 48 of PEG-IFN

Baseline HBsAg <1,500 IU + wk-12 HBsAg <200 IU/ml = PPV 51%
Switch to” Peg-IFN long-term NUC CHB patients
The Japanese Red Cross Hospital Liver Study Group

49 NUC patients were switched to 48-week PEG-IFN vs 147 NUC patients

- HBsAg reduction at week 48 was 0.81±1.1 log IU/mL in IFN group, and 0.11±0.3 log IU/mL, in the NUC group (P < .001).
- Treatment response, defined as HBsAg reduction ≥1.0 logIU/ml, was achieved in 29% and 2% of the IFN group and NUC group (P < .001).
- In HBeAg pos pts, HBeAg seroconversion was higher in the sequential group (44% vs 8%, P < .001).
- In HBeAg-negative patients, only patients switched to IFN achieved HBsAg loss.
- No patient needed to restart NA because of HBV DNA increase and ALT flares.
- HBsAg decline at week 12 of 0.2 log IU/mL was the best predictor of response (AUROC 0.96, PPV 72%, NPV 97%..

HBsAg <100 IU/mL 35% vs 15%, p=0.002
HBsAg loss: 4% vs 0%, p=0.01

Tamaki N et al, JVH 2017
“Add-on” PEG-IFN alfa-2b in HBeAg pos NUC treated pts: A Randomized, Controlled Trial from China (PEGON)

77 HBeAg positive patients with HBV DNA <2,000 IU/ml on ETV/TDF randomized to 48-week add-on Peg-IFN (n = 39) or continued NA monotherapy (n = 38)

Chi H et al, JID 2017
“Add-on” PEG-IFN in HBeAg neg NUC responders
On-treatment changes in HBsAg levels

Mean HBsAg titer log10 (IU/ml)

-0.19*
-0.91*

-0.35*
-0.89*

W0 W12 W24 W36 W48 W60 W72 W84 W96

Weeks

HBsAg loss: 0%*

HBsAg loss: 3%**

Bourliere M. et al, Lancet GH 2017

*p=0.0057
**p=0.1521

Log10 IU/ml decrease between W0/W48 and W0/W96. Error bars represent 95% confidence intervals.
“Add-on” Peg-IFN in HBeAg neg, geno D, NUC responders
The HERMES study

(70 patients - Week 48 analysis)

Overall, 73% qHBsAg decline (0.6 log IU/ml decline)
43% with >50% HBsAg decline
20% with HBsAg <100 IU/ml
3% with HBsAg <10 IU/ml
One HBsAg loss (1.4%)

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, submitted 2018
Standard and New markers for HBV

**Standard markers:**
- qHBsAg
- HBeAg/anti-HBe
- HBV-DNA levels
- Anti-HBc

**New markers:***
- ultra sens qHBsAg
- HBeAg levels
- ultra sens HBV-DNA
- Anti-HBc levels
- HBcrAg
- HBV-RNA levels
- Different HBsAg proteins

* No commercially available assays available
Summary and Conclusions

- Peg-IFN is a standard of care therapy for HBV
- 20-30% of naïve patients benefit from this strategy
- The long-term outcome of these responders is very good
- Baseline prediction scores and week 12 stopping rules have been developed (host genetics?)
- Peg-IFN could also be used to accelerate HBsAg kinetics in NUC treated patients (add-on, switch to……)
- New HBV biomarkers could be useful in the IFN setting