How do I treat my HBeAg-positive patients?

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Je suis Charlie
When do I treat my HBeAg-positive patients?
Antiviral therapy in HBeAg(+) patients with PNALT

• Maintenance of high HBV replication: increasing numbers of infected hepatocytes, risk of progression of liver lesions, increasing HCC risk

• High risk of HBV transmission

• Usually minimal histological lesions
• Immune tolerance – Low probability of anti-HBe seroconversion
• (Peg-)IFNa: not effective - NAs: inhibition of HBV replication
• Probably life-long therapy in young patients: long-term safety, family planning?
Indications for treatment in HBeAg+ patients

• ALT >2xULN & HBV DNA >20,000 IU/ml
  Treatment (Biopsy optional)

• ALT 1-2xULN and/or HBV DNA 2,000-20,000 IU/ml
  Biopsy – Treatment in patients with ≥moderate histol. lesions

• ALT <ULN regardless of HBV DNA levels
  Usually no treatment – Biopsy?

• Indications for treatment may also take into account age, health status, family history of HCC or cirrhosis and extrahepatic manifestations

EASL HBV CPGs. J Hepatol 2012;57:167-85
Management of HBeAg-positive patients with high HBV DNA (>20,000 IU/mL) and PNALT

- Age >40 years: treatment
- Age 30-40 years: decisions individualised - liver biopsy
- Age <30 years: follow-up (ALT /3-6 mos, HBeAg/anti-HBe /6-12 mos)
- Positive family history for HCC: reduce the age limit for treatment initiation
- Clinical or laboratory indications of advanced liver lesions (eg low PLT, high gamma-globulins, splenomegaly, spiders, palmar erythema, advanced fibrosis by noninvasive markers etc): liver biopsy even in patients <30 years

Potential additional treatment indications
- Immunosuppression/Chemotherapy
- Professional reasons
- Last trimester of pregnancy

EASL HBV CPGs. J Hepatol 2012;57:167-85
TDF vs TDF+FTC x192 wks in HBeAg+ patients with normal ALT and high HBV DNA

Mean age: 33 years; 89% Asians, 93% gen. B/C, mean HBV DNA: $8.4 \log_{10} \text{IU/mL}$

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<tr>
<th>Outcome at week-192</th>
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HL Chan et al. Gastroenterology 2014;146:1240-8
### TDF vs TDF+FTC x192 wks in HBeAg+ patients with normal ALT and high HBV DNA

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<tr>
<td></td>
<td></td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>HBV resistance</td>
<td>0%</td>
<td>0%</td>
<td>NS</td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
<td>5%</td>
<td>0%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>29%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>0%</td>
<td>0%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>11%</td>
<td></td>
<td></td>
</tr>
</tbody>
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TDF x192 wks in HBeAg+ CHB: Heathcote EJ et al. AASLD 2010, Abstr. 477
HL Chan et al. Gastroenterology 2014;146:1240-8
How do I treat my HBeAg-positive CHB patients?
HBV-RELATED CHRONIC LIVER DISEASE

Groups of treatment options

(Peg)-IFNa
(antiviral+ immunomodulator)

ETV, TDF
TBV, LAM, ADV
(pure antivirals)
HBV-RELATED CHRONIC LIVER DISEASE

THERAPEUTIC INDICATIONS

(Peg-)IFNa or Nucleos(t)ide analogue(s) [NA(s)]

• Chronic hepatitis B (including compensated cirrhosis)

Only NA(s)

• Decompensated HBV cirrhosis
• Prophylaxis in HBV transplant cases
• Pre-emptive therapy in inactive HBV carriers receiving immunosuppressive/chemo-therapy
• Pregnant women with high HBV viremia
• Health care workers in the HBV immunotolerant phase
Peg-IFNa for HBeAg+ CHB

- 48 weeks of therapy
- 30-32% HBeAg seroconversion
- 80-90% long-term durability of response off-therapy
- 12-15% (~50% of responders) HBsAg clearance after 5 years
- Improved histology & long-term outcomes in sust. responders

Baseline and/or on-therapy predictors of response
(HBeAg seroconversion & low HBV DNA)?
NA(s) for HBeAg+ CHB

- HBeAg seroconversion: 20% at year 1, 40-50% at year 5
- On-therapy HBV DNA undetectability in >95% of compliant patients under ETV or TDF (first-line options)
- No/negligible risk of resistance with ETV (1%) or TDF (0%)
- 10-12% HBsAg loss at year 5 – no major increase until year 8
- Improved histology & long-term outcomes

Durability of off-NA response (anti-HBe seroconv. & low HBV DNA)?
Baseline and/or on-therapy predictors of response?
Baseline predictors of response (anti-HBe seroconversion) in HBeAg+ CHB patients
Baseline predictors of response (anti-HBe seroconversion) in HBeAg+ CHB patients

Similar for Peg-IFNa and NAs

• Higher ALT

• Lower HBV DNA

• Higher histological activity

• HBV genotype A > D & B > C (better predictors for Peg-IFNa)
Baseline predictors of response to Peg-IFNa (HBeAg loss & HBV DNA<10,000 cp/ml) in HBeAg+ CHB

Pts, n
Gen. A=115
Gen. B=166
Gen. C=333
Gen. D=107

Buster EHCJ et al. Gastroenterology 2009;137:2002-9
Baseline predictors of response to Peg-IFNa-2a (anti-HBe seroconversion) in HBeAg+ CHB

**Baseline (BL) Score:** Female (+1); HBsAg<20,000 IU/mL (+1); HBV genotype A (+2); ALT 1.5-<4xULN (+1), ALT≥4xULN (+2); HBV DNA (log\(_{10}\) IU/mL) 8-<10 (+1), HBV DNA<8 (+2)

<table>
<thead>
<tr>
<th>BL Score</th>
<th>0-1</th>
<th>2-3</th>
<th>4</th>
<th>5</th>
<th>≥6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, %</td>
<td>10</td>
<td>46</td>
<td>30</td>
<td>12</td>
<td>2</td>
</tr>
</tbody>
</table>

Patients, n=443

HLY Chan et al. AASLD 2014, Abstr. 1886
On-treatment predictors of response (anti-HBe seroconversion) in HBeAg+ CHB patients
On-treatment predictors of response (anti-HBe seroconversion) in HBeAg+ CHB patients

Clinically meaningful

• Only for Peg-IFNa
• Not for NAs (used as both finite duration and maintenance therapy)

Meaningful for NAs: on-treatment predictors of HBsAg loss
Peg-IFNα stopping rules

• HBeAg+ve: HBsAg levels $\geq 20,000$ IU/mL or no decline in HBsAg levels by month 3 (C2)
  
  Piratvisuth et al. APASL 2010; Gane et al. EASL 2011; Sonneveld et al. Hepatology 2010
  
  EASL HBV CPGs. J Hepatol 2012;57:167-85

HBsAg levels as a positive predictor of response to Peg-IFNα

• HBeAg+ve: HBsAg levels $< 1,500$ IU/mL at 12 or 24 wks
  
  = probability of anti-HBe seroconversion $> 50%$

  Piratvisuth et al. APASL 2010; Gane et al. EASL 2011
Peg-IFNa stopping rules

- HBeAg+ve: HBsAg levels $\geq 20,000$ IU/mL (better predictability in genotype B or C*) or no decline in HBsAg levels by month 3 (better predictability in genotype A or D*) (C2)

Post-NA(s) durability of anti-HBe seroconversion
Post-therapy durability of HBeAg seroconversion

- **Spontaneous Taiwan**: 271/283 (Hsu, 2002)
- **IFNa Caucasian Taiwan**: 29/31 (Lau, 1997)
- **Peg-IFNa Caucas. Chinese**: 69/71 (Lin, 2007)
- **Peg-IFNa Caucas. Chinese**: 52/64 (Buster, 2008)
- **Peg-IFNa Caucas. Chinese**: 22/27 (Wong, 2010)
- **Asian**: 30/36 (Leung, 2001)
- **Caucas.**: 30/39 (Dienstag, 2003)
- **LAM Asian**: 42/95 (Yoon, 2005)
- **Mixed**: 13/42 (Reijnders, 2010)

Median f-up (mos): 103, 83, 82, 36, 60, 20, 37, 24, 59
Variability in the rates of durable anti-HBe seroconversion induced by NAs

- Anti-HBe seroconversion not always accompanied by HBV DNA undetectability at NA(s) discontinuation
- Variable durations of consolidation therapy after anti-HBe seroconversion
- Variable definitions of post-NA(s) response
Clinical significance of relapse following NA(s) discontinuation in initially HBeAg+ CHB patients

• NO DATA for dramatic events in non-cirrhotic patients who discontinued NA(s)

• Patients who fulfill the standard treatment indications can be always retreated
When can we consider stopping NA therapy in HBeAg+ CHB?

• All international guidelines: stop NAs after HBeAg seroconversion & undetectable HBV DNA & 6–12 months consolidation\(^1\text{-}^3\)

• EASL: perhaps continue until HBsAg loss (i.e. potentially indefinitely) particularly in severe fibrosis/cirrhosis due to high risk of relapse\(^1\)

Main predictors of HBsAg loss after 3 years of TDF in HBeAg+ CHB patients

- Non-Asian race
- Genotype A
- Higher baseline necroinflammatory activity
- Higher baseline HBsAg levels (median: 5.11 vs 4.50 log IU/ml)
- Greater change in HBsAg levels at week 24 (median: 2.41 vs 0.20 log IU/mL)

EJ Heathcote et al. Gastroenterology 2011; 140: 132-43
Is there a role for Peg-IFNa and NA(s) combination for HBeAg+ CHB?
**TDF +/- Peg-IFNa-2a in CHB**

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>16</th>
<th>24</th>
<th>48</th>
<th>72</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>58%</td>
<td>n=186</td>
<td>TDF + PEG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>58%</td>
<td>n=184</td>
<td>TDF+PEG → TDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60%</td>
<td>n=185</td>
<td>TDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>58%</td>
<td>n=185</td>
<td>PEG</td>
<td></td>
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Start TDF during follow-up if prespecified safety criteria met

- 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

P Marcellin et al. AASLD 2014
HBsAg Loss Over Time (Week 72)

7 patients had HBsAg seroreversion on or after Week 48 (4 [TDF + PEG 48 wk], 3 [TDF + PEG 16 wk → TDF 32 wk])

- 5/7 had ≤1 week of therapy after HBsAg loss

P Marcellin et al. AASLD 2014
HBeAg seroconversion rates (Weeks 48 & 72)

Patients with anti-HBe seroconversion, %

- TDF+PEG 48 wk: 23.1, 25%
- TDF+PEG 16 wk → TDF 32 wk: 19, 23.8%
- TDF 120 wk: 8.3, 12.8%
- PEG 48 wk: 12.3, 24.5%

P Marcellin et al. AASLD 2014
No clear role for Peg-IFNa and NA(s) combination in the current management of HBeAg+ CHB
HBeAg-positive CHB patients

Peg-IFNa
(preferred candidates: young patients with high ALT, low HBV DNA, genotype A or B)

On treatment monitoring
ALT, HBsAg, HBeAg, HBV DNA

Quantitative HBsAg at week 12

HBsAg <1500 IU/ml:
high chance of anti-HBe seroconversion

Peg-IFNa for 48 weeks

Response*

Continue follow-up with ALT, HBeAg/anti-HBe, HBsAg, HBV DNA

No response*

Treat with NAs

No decline from baseline (genotype A or D) or HBsAg >20000 IU/ml (genotype B or C)

Stop Peg-IFNa - Switch to NAs

Vlachogiannakos & Papatheodoridis. Liver Intern 2015
HBeAg-positive CHB patients

**Peg-IFNa**
(preferred candidates: young patients with high ALT, low HBV DNA, genotype A or B)
- On treatment monitoring
  - ALT, HBsAg, HBeAg, HBV DNA
  - Quantitative HBsAg at week 12
    - HBsAg <1500 IU/ml: high chance of anti-HBe seroconversion
      - Peg-IFNa for 48 weeks
        - Response*
          - Continue follow-up with ALT, HBeAg/anti-HBe, HBsAg, HBV DNA
        - No response*
          - Treat with NAs
    - No decline from baseline (genotype A or D) or HBsAg >20000 IU/ml (genotype B or C)
      - Stop Peg-IFNa - Switch to NAs
      - Continue treatment for 12 more months and follow the patient
      - No seroconversion to anti-HBe or detectable HBV DNA
      - Monitor HBsAg - Continue treatment until HBsAg loss

**NAs (ETV or TDF)**
- On treatment monitoring
  - ALT, HBeAg, HBV DNA
- HBV DNA at week 48
  - HBV DNA undetectable or declining
    - Seroconversion to anti-HBe and HBV DNA undetectable
      - Continue treatment indefinitely
    - Continue treatment for 12 more months and follow the patient
  - HBV DNA not declining
    - Check compliance, switch/add the other NA
      - Check ALT, HBeAg, HBV DNA every 6 months
      - No seroconversion to anti-HBe or detectable HBV DNA

Response*

Treat with NAs

No response*

Vlachogiannakos & Papatheodoridis. Liver Intern 2015
Thank you for your attention!