Clinical dilemmas in HBeAg-negative CHB

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Case 2

- 9/2008 - Asymptomatic Greek, 30 year-old, man
- HBsAg+ during blood donation 3 years ago
- ALT: 32-38 IU/L, AST: 12-26 IU/L on 3 occasions over last 3 years
- LFTs, FBC, PT: normal
- HBeAg-, anti-HBe+, anti-HCV-, anti-HDV-, anti-HIV-, anti-HAV+
- No other disease, no family history of liver disease
- Social drinking (<15 g alc/day), Smoker (20 cig./day x14 years)
- Normal physical examination, BMI: 23.5 kg/m2
- Abdominal U/S: normal

ULN for ALT/AST: 40 IU/L
Case 2 - follow-up

- **10/2008** – ALT 42 IU/L, AST 32 IU/L
- HBV DNA 2800 IU/mL
- Fibroscan-stiffness: 7.0 kPa

- **11/2008-03/2009** – ALT 36, 48 and 40 IU/L on 3 occasions
- HBV DNA 4200 IU/mL
- Serum HBsAg 3400 IU/mL

ULN for ALT/AST: 40 IU/L
Case 2 - Summary

- HBeAg- patient
- Normal - Mildly elevated ALT (<1.2xULN)
- Moderate HBV DNA (2000-20000 IU/mL)
- High HBsAg levels (>1000 IU/mL)
- Moderate stiffness
- Reluctant for liver biopsy
Case 2 – Question

How would you manage this patient?

1. Further follow-up with ALT & HBV DNA
2. Start Peg-IFNa
3. Start LAM
4. Start ETV or TDF
HBV DNA, Elastographic (LSM) and histological findings in 182 HBeAg-negative patients with PNALT & HBV DNA <20000

% of 182 inactive carriers

≥moderate fibrosis in 30 inactive carriers with HBV DNA >2000 IU/mL and/or LSM>6.5 kPa, %

P=0.009

LSM: liver stiffness measurements, PNALT: persistently normal ALT

HBeAg-negative patient with normal ALT at baseline

ALT every 3–4 months for one year + serum HBV DNA determination

- ALT > ULN and/or
- HBV DNA > 20,000
  - Liver biopsy

Persistently ALT < ULN and
HBV DNA 2,000–20,000

ALT every 3–4 months
and HBV DNA every year
for two more years (FibroScan?)

- ALT < ULN and HBV DNA 2,000–20,000 IU/mL
  - ALT every 6 months
  - ALT < ULN and HBV DNA 2,000–20,000 IU/mL
    - ALT every 6 months and HBV DNA every year
      - ALT > ULN and/or
      - HBV DNA > 20,000
        - Liver biopsy

Persistently ALT < ULN and
HBV DNA < 2,000 IU/mL

ALT every 6 months
(& HBV DNA?)

Probability of progression from inactive carrier state to HBeAg-negative chronic hepatitis B

**Baseline serum HBV DNA ≥2,000 IU/mL**

**Baseline serum HBV DNA <2,000 IU/mL**

**Patients at risk**

<table>
<thead>
<tr>
<th>HBV DNA ≥2,000 IU/mL</th>
<th>20</th>
<th>20</th>
<th>9</th>
<th>6</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA &lt;2,000 IU/mL</td>
<td>65</td>
<td>65</td>
<td>30</td>
<td>26</td>
<td>6</td>
</tr>
</tbody>
</table>

Case 2 – Further follow-up

- **04-10/2009** - ALT 32 and 145 IU/L on two 3-monthly determinations
- **11/2009** - ALT 220 IU/L

- **10/2009** - HBV DNA 245,000 IU/mL
  - HBsAg 3800 IU/mL
  - Fibroscan - stiffness 10.2 kPa

- Treatment initiation (without a liver biopsy) was decided
Possibility for treatment initiation without liver biopsy

- **Patients with obviously active CHB:** HBeAg+ve and HBeAg-ve patients with ALT >2xULN and HBV DNA >20,000 IU/mL (B1).

Liver biopsy additional useful information, but not usually change treatment decision.

A non-invasive method to confirm or rule out cirrhosis is extremely useful in patients who start treatment without liver biopsy (B1).

EASL HBV CPGs, 2012
Case 2 – Question

Which therapeutic agent would you prefer?

1. Peg-IFNa
2. LAM
3. ETV or TDF
4. Other
Optimal first-line therapy in compensated CHB (A1)

**Peg-IFNa (IFNa)**
- Young (reproductive) age
- Favorable factors of response
  - HBeAg(+)CHB: low HBV DNA, high ALT, genotype A vs D or B vs C
  - HBeAg(-)CHB: unknown
- Patient’s preference

**ETV/TDF (TBV, ADV, LAM)**
- Not candidates for IFNa
- Contraindication for IFNa
- No sustained response with IFNa
- Patient’s preference

EASL HBV CPGs, 2012
Case 2 - Question

• 11/2009 – Peg-IFNa-2a 180 μg/week  
  Good tolerability

• At 12 weeks: ALT 65 IU/L  
  HBV DNA 650,000 IU/mL  
  HBsAg 2800 IU/mL

• Would you continue Peg-IFNa?  
  – Yes  
  – No
PegIFN stopping rule

- **HBeAg-ve (genotype D):** no decline in **HBsAg levels** and no **HBV DNA** drop ≥2 log10 IU/mL by month 3 (B2)
Case 2 - Question

• Peg-IFNa-2a continued - Good tolerability

• 11/2010 (48 weeks): ALT 35 IU/L
  HBV DNA 1,200 IU/mL
  HBsAg 1600 IU/mL

• Would you continue Peg-IFNa?
  - Yes
  - No
Case 2 - Question

• Peg-IFNa-2a stopped

• **01/2011**: ALT 95 IU/L, HBV DNA 125,000 IU/mL

• **02/2011**: ALT 165 IU/L, HBV DNA 825,000 IU/mL

Retreatment was decided.

• Which agent would you recommend?
  – Peg-IFNa
  – LAM
  – ETV or TDF
  – Other
Case 2 - Question

- **02/2011**: TDF monotherapy started

- How often would you monitor HBV DNA?
  - At 3 and 6 and then every 6 months
  - Every 6 months
  - At 6, 12 and then every 12 months (if HBV DNA undetectable)
HBV monitoring during therapy with NAs

Finite treatment with NAs in HBeAg+ve patients

- **HBV DNA** every 3 mos
- **HBeAg/anti-HBe** every 6-12 mos
- NA therapy can be stopped 12 mos after anti-HBe seroconversion (B1)
- **HBsAg** every 6 mos after anti-HBe seroconversion
- NA treatment may be continued until HBsAg clearance with or without anti-HBs, particularly in patients with severe fibrosis or cirrhosis (C1)

Long-term therapy with NAs

- HBV DNA undetectability by PCR (<10–15 IU/ml) should ideally be achieved to avoid resistance (A1)
- **HBV DNA** at 3 and then every 3-6 mos
- **During ETV or TDF therapy**, the frequency of HBV DNA follow-up may be decreased when patient compliance and treatment efficacy have been established (C1)

EASL HBV CPGs, 2012
Case 2 - Question

• 02/2011: TDF monotherapy started
• How often would you recommend renal safety monitoring?
  – Every month for 1st 3 months and every 3 months thereafter
  – Every 3 months for 1st year and every 6 months thereafter
  – Every 6 months for 1st year and every 12 months thereafter
Case 2 - Question

- **02/2011**: TDF monotherapy started
- Which safety monitoring would you recommend?
  - Serum creatinine (eGFR)
  - Serum creatinine (eGFR) & phosphate
  - Serum creatinine (eGFR) & phosphate, urine analysis
  - Serum creatinine (eGFR) & phosphate, urine analysis, bone density
## Renal monitoring during NAs

<table>
<thead>
<tr>
<th>Renal risk</th>
<th>Antiviral</th>
<th>Test (C1)</th>
<th>Frequency (C2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>ADV, TDF</td>
<td>Clcr, Serum phosphate</td>
<td>0, 3, 6, 9, 12 &amp; then every 6 mos</td>
</tr>
<tr>
<td>High</td>
<td>ADV, TDF</td>
<td>Clcr</td>
<td>0, 1, 2, 3, 6, 9, 12 &amp; then every 6 mos</td>
</tr>
<tr>
<td></td>
<td>LAM, ETV, TBV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Case 2 - Question

- **02/2011**: TDF monotherapy started
- Would you recommend HCC surveillance with U/S?
  - Yes
  - No
PAGE-B: a simple HCC risk score for the first 5 years of ETV/TDF therapy in Caucasian CHB patients

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender</th>
<th>Platelets (/mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16–29: 0</td>
<td>Female: 0</td>
<td>≥200,000: 0</td>
</tr>
<tr>
<td>30–39: 2</td>
<td>Male: 6</td>
<td>100,000–199,999: 6</td>
</tr>
<tr>
<td>40–49: 4</td>
<td></td>
<td>&lt;100,000: 9</td>
</tr>
</tbody>
</table>

**Our case – PAGE-B: 8**
Males ≥40 yrs, females ≥70 yrs, PLT <200,000/mm³:
moderate to high HCC risk (PAGE-B ≥10)

**HCC risk**
Low (or no) – PAGE-B<10, Intermediate -PAGE-B=10-17, High –PAGE-B>17

Papatheodoridis GV et al. J Hepatol 2016, in press
Case 2 - Question

• 01/2016: TDF monotherapy continued
  • ALT<ULN & HBV DNA undetectable since 07/2011
  • HBsAg 3120 IU/mL
  • Would you consider discontinuation of TDF?
    − Yes
    − No
Rates of virological remission after NAs discontinuation

17 studies, 967 HBeAg- patients

Pooled HBsAg loss: 1.7%; Durable biochemical remission: 57%

GV Papatheodoridis et al. Hepatology 2016; accepted manuscript
Case 2 - Questions

If TDF stopped, issues for discussion

- Role of HBsAg levels
- Add-on or switch to Peg-IFNa during the last period of TDF?
- Optimal follow-up after TDF?
- Criteria for retreatment?
- Type of retreatment?
Case 1

• 9/2012 - Asymptomatic Greek, 47 year-old, man
• HBsAg+ diagnosed at blood donation 3 months ago
• ALT: 35 IU/L, AST: 22 IU/L, LFTs, FBC, PT: normal
• HBeAg-, anti-HBe+, anti-HCV-, anti-HIV-, anti-HAV+
• No other disease, no family history of liver disease
• No alcohol, no smoking
• Normal physical examination, BMI: 28.7 kg/m2
• Abdominal U/S: normal

ULN for ALT/AST: 40 IU/L
HBeAg- patients with normal baseline ALT

Inactive chronic HBV carriers
(good long-term outcome)
Don’t treat – Follow-

Patients with HBeAg-negative CHB
(progressive liver disease)
Treat
Case 1 - follow-up

• **10/2012** - ALT 62 IU/L, AST 42 IU/L
• HBV DNA 1,800 IU/mL, anti-HDV-
• Fibroscan-stiffness: 7.2 kPa

• **11/2012-03/2013** – ALT 68, 98 and 54 IU/L on 3 occasions
• Negative autoantibodies
• Ferritin 150 μg/L
• HBV DNA 980 IU/mL
• Serum HBsAg 320 IU/mL

ULN for ALT/AST: 40 IU/L
Case 1 – Question

What do you think for this patient?

1. He is an inactive chronic HBV carrier
2. He has HBeAg-negative CHB
3. He needs HBV therapy
4. He needs a liver biopsy
Case 1 - Summary

- HBeAg- patient
- Elevated ALT (occasionally >2xULN)
- Moderate liver stiffness
- Low HBV DNA (<2000 IU/mL)
- Low HBsAg levels (<1000 IU/mL)
Follow-up of HBeAg– patients with persistently normal ALT & HBV DNA <2000 IU/mL

• HBsAg ≥1000 IU/mL: every 6 months

• HBsAg <1000 IU/mL: every 12 months?

Case 1 – Elevated ALT: Need for liver biopsy

• **04/2013** -Liver biopsy: lesions of NASH with mild activity, mild fibrosis and mild severity of steatosis

**Chronic HBV infection:**

HBV is usually but not always the cause of liver injury