Clinical applications of HBsAg quantification

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Do you perform HBsAg quantification during the follow up of

- Interferon treatment
- NAs treatment
Clinical case

Female, 35 yrs, chinese

- ALT 126 IU/L (N=40)
- HBeAg (-)
- HBV DNA = 200 000 UI/mL
- HBsAg = 6050 UI/mL
- Liver biopsy: A2 F2
# Clinical Case

<table>
<thead>
<tr>
<th></th>
<th>D0</th>
<th>M6</th>
<th>Y1</th>
<th>Y3</th>
<th>Y3.5</th>
<th>Y5</th>
<th>Y7</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>166</td>
<td>62</td>
<td>40</td>
<td>40</td>
<td>38</td>
<td>29</td>
<td>32</td>
</tr>
<tr>
<td>HBs Ag</td>
<td>6050</td>
<td>5880</td>
<td>6288</td>
<td>5900</td>
<td>120</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HBVDNA</td>
<td>200000</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>&lt;20</td>
</tr>
</tbody>
</table>

- **ENTECAVIR 0.5mg/D**
- **PEG-IFN**
How do the available therapies work?

**OFF-TREATMENT**
Immune control and HBsAg clearance

**SUSTAINED RESPONSE**
Through Immunomodulatory and antiviral mode of action

**FINITE** therapy

**ON-TREATMENT**
Viral suppression

**MAINTAINED** suppression
Through continued therapy

**LONG-TERM** therapy
(Potentially life-long for some)

**INTERFERON**

**NAs**
HBsAg loss after 1 and 2-5 ans of treatment

Peg = peginterferon
LAM = lamivudine
ADV = adefovir
ETV = entecavir
LdT = telbivudine
TDF = tenofovir

^ 3-4 Years off Rx
# 4-5 Years on Rx

4. Heathcote J, Hepatology, 2008;48(4)suppl1:376A.
- Average decline/year $0.141 \log_{10}$
- Median time for HBs Ag loss = 52.1 years (Q1-Q3: 24.5-117.6)

Chevaliez et al., J. Hepatol 2013: 58, 641-642
Prediction of outcome

Prediction of outcome after NUCs therapy discontinuation (2 measurements with HBeAg or ADN negative)

Cumulative probability of virological relapse

- HBsAg >3 log IU/ml at end of therapy
- HBsAg 2-3 log IU/ml at end of therapy
- HBsAg ≤ 2log IU/ml at end of therapy

Detectable HBV DNA at W12
- p=0.03

Undetectable HBV DNA at W12
- p=0.01

HBsAg ≤ 2log IU/ml at treatment discontinuation is predictive of sustained response

➢ Define optimal HBsAg thresholds that enable treatment discontinuation with low risk of relapse
Off-Therapy Durability of Response to Entecavir in Hbe Ag negative chronique hepatitis Patients

- 95 patients (39 F4*) treated with ETV for 721 days (395-1762) before discontinuation (APASL guidelines)

- Within 1 year after stopping Relapse in 43 (45%) patients 23% vs. 53% according to baseline HBVDNA < or > 2X10^5 UI/ML

*1 decompensation

Jeng WJ et al. Hepatology 2013;6:1888-95
Predicting response with HBsAg levels: HBeAg-positive patients
NEPTUNE confirms association of on-treatment HBsAg level with response to PEGASYS

HBeAg-positive patients treated with PEGASYS for 48 weeks

Motivate patients to continue

Liaw et al. Hepatology 2011
HBeAg-positive patients treated with PEGASYS for 48 weeks

Seroconversion rates at 6 months post-treatment:

**Week 12**
- Low (<1500): 58%
- Medium (1500–20,000): 42%
- High (>20,000): 6%

**Week 24**
- Low (<1500): 57%
- Medium (1500–20,000): 35%
- High (>20,000): 0%

Potential early stopping rule

Sooneveld et al. Hepatology 2013; 58: 872-80
Predicting response with HBsAg decline: HBeAg-negative patients
Early HBsAg kinetics between relapsers and responders

HBV DNA and HBsAg Kinetics

Combining HBsAg and HBV DNA decline for early identification of non-response

Analysis of 102 patients with available HBV DNA and HBsAg levels (80% genotype D)

WEEK 12

ANY HBsAg decline

HBV DNA decline (copies/mL)

Sustained response*

*HBV DNA <10,000 copies/mL and ALT normal 6 months post-treatment

Rijckborst et al. Hepatology 2010;52:,454--61
**Prediction at end of treatment**

**SVR and HBsAg loss**

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**Week 48 HBsAg titer**

<table>
<thead>
<tr>
<th>Sustained Virological Response</th>
<th>HBsAg IU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>80%*</td>
<td></td>
</tr>
<tr>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*52% HBsAg loss at 3 yrs versus 2% if > 10 UI/ml

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**End of treatment HBsAg threshold**

- **Prediction of SVR**
  - **Genotype A**: $< 400$ UI, PPV = 75%, NPV = 100%
  - **Genotype B**: $< 50$ UI, PPV = 47%, NPV = 100%
  - **Genotype C**: $< 75$ UI, PPV = 70%, NPV = 80%
  - **Genotype D**: $< 1000$ UI, PPV = 75%, NPV = 82%

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**On-treatment kinetics of HBsAg serum levels vary by HBV genotype**

*Brunetto et al. Hepatology 2009;49:1141* 
*Brunetto et al. J of Hepatol 2013.;59 :153-59*
## On-Treatment HBsAg as Marker of Response to PegIFN

### 120 HBeAg-patients treated with PEG-IFNα-2a during 48 sem

<table>
<thead>
<tr>
<th>Decline in HBsAg titers ≥ 10%</th>
<th>Percentage of patients</th>
<th>HBs Ag loss at 5 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Continious</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J0 à W24 yes → yes</td>
<td>51%</td>
<td>23%</td>
</tr>
<tr>
<td>W24 à 48 yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Late</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no → yes</td>
<td>16%</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Early</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes → no</td>
<td>5%</td>
<td>17%</td>
</tr>
<tr>
<td><strong>Any decline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no → no</td>
<td>28%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Brunetto MR et al. AASLD 2009*
Extending duration of Pegasys treatment increase response rate in HBe negative patients: PegBeLiver study

Patients with HBsAg <1000 IU/ml at week 48 had response rates of 25% vs 80%, depending on the treatment duration (48 vs. 96 weeks)

On-Treatment HBsAg as Marker of Optimal duration of PegIFN in patients with chronic hepatitis B+D

Overall decline in HBsAg is greater for PEG-IFN vs NAs

No significant decline of HBsAg with 1 year of ETV in HBeAg-negative patients

Reijnders et al. J Hepatol 2011; 54,449-54
Brunetto et al. Hepatology 2009; 49,1141-50
PEGIFN 48 weeks: virological response at 5 years

Reduction of HBV replication prolongs the early immunological response to IFN therapy

**Marcellin P et al, Hepatol Int. 2013; 7:88-97**

**Tan AT et al, J of Hepatol. 2014; 60:54-61**
Add-on of peg interferon to a stable nucleoside regimen led to loss of HBs Ag in chronic hepatitis HBe Ag negative patients

10 HBe negative consecutive patients treated with NUCs during (3-7yrs)

HBVDNA <20UI/ml in all patients since more than three years

These patients received additional peginterferon alpha2a treatment during 96 weeks
### HBsAg titers (UI/ml) during add-on PEG IFN and 6 to 18 months later

<table>
<thead>
<tr>
<th>Metavir</th>
<th>NUCs treatment before PegIFN</th>
<th>J0</th>
<th>W48</th>
<th>W96</th>
<th>W120</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2F2</td>
<td>ADV (6 ans)</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>A2F3</td>
<td>LAM (8 ans)</td>
<td>123</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>A3F3</td>
<td>ADV (7 ans)</td>
<td>248</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>A1F1</strong></td>
<td>ADV (6 ans)</td>
<td>789</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>A3F3</td>
<td>ADV+ETV (8 ans)</td>
<td>110</td>
<td>87</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>A2F2</td>
<td>ETV (3 ans)</td>
<td>6050</td>
<td>120</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>A2F4</td>
<td>ETV+ADV (6 ans)</td>
<td>530</td>
<td>380</td>
<td>120</td>
<td>130</td>
</tr>
<tr>
<td>A1F2</td>
<td>ADV+ETV (7 ans)</td>
<td>974</td>
<td>40</td>
<td>115</td>
<td>115</td>
</tr>
<tr>
<td>A1F1</td>
<td>LAM+TFV (3 ans)</td>
<td>1320</td>
<td>345</td>
<td>120</td>
<td>100</td>
</tr>
<tr>
<td>A2F4</td>
<td>LAM+ADV (8 ans)</td>
<td>1754</td>
<td>1380</td>
<td>1100</td>
<td>1000</td>
</tr>
</tbody>
</table>
HBs Ag titer decline in four patients who reached negative values at W48

HBsAg loss in 4 patients: HBs Ag Séroconversion in 2 patients
HBs Ag titers decline in 6 patients who received (but one) Peg IFN treatment during 96 weeks.
Add-on of peg interferon to a stable nucleoside regimen

• In patients, long term fully suppressed by NUCs, add-on of PegIFN, allows HBsAg loss in 6/10 patients.

• HBsAg titers decline constitute a useful tool which predicts the loss of HBsAg

• HBsAg titers decline may lead to definite the optimal duration of IFN therapy.
Add-on of peg interferon to a stable nucleoside regimen

12 patients (HBeAg - : 9/12)

HBV DNA undetectable in all patients treated with NucS

Add on PEGIFN improves HBs Ag kinetics in patients long term fully suppressed by Nucs

- 12 patients (HBeAg - : 9/12)
- HBV DNA undetectable in all patients treated with NucS

HBsAg titers decrease in 5 patients HBeAg - treated more than 6 months
Add-on of peg interferon to a stable nucleoside regimen

- **NUCs**
- **Pegasys 180 µg 48 weeks**
- **Analogues 48 weeks**
- **Analogues 96 weeks**
- **Analogues 144 weeks**

30 centers

Assessment of HBsAg loss

Randomisation

≥ 1 an

*HBV DNA undetectable
HBsAg quantification

- HBs Ag quantification has to be included in the follow up of all patients treated for hepatitis B
- This assay together with HBVDNA predict treatment response, optimal duration of interferon treatment
HBsAg quantification

✓ A viral suppression can be provided today to all patients and it is the primary goal in clinical practice

✓ HBsAg loss became the next goal and depend of
  • HBs Ag quantification
  • Evaluation of new strategies: combination of antiviral and immune therapy
Hepatitis B surface antigen quantification: Why and how to use it in 2011
A core group report


for the Good Practice in using HBsAg in Chronic Hepatitis B Study Group (GPs-CHB Study Group)