HBsAg quantification to monitor patients

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HBsAg quantification is now a hot topic

Dev Biol Stand 1975;30:78-87
Standardized detection of hepatitis B surface antigen: determination of its serum concentration.
Gerlich W Thomseen R.

Digestion 1987;38(2):90-95
Detection of hepatitis B virus markers in sera of asymptomatic hepatitis B carriers.

Antiviral research 1994;23(3):251-257
Measurement of HBsAg to monitor hepatitis B patients treated with interferon.
Jansen HL, Shalm SW.

Hepatology 2009;49:1151-1157
Early serum HBsAg drop: a strong predictor of sustained virological response.
Moucari R, Mackiewicz V, Lada O, Ripault MP, Castelnau C, Martinot-Peigno

Commercially available assays


> 120 congresses
> 500 articles in key journals
Significance of HBsAg in serum

The levels of serum HBsAg (qHBS):

- Reflect the balance between the virus and the host immune response.
- Dependent of the amount and transcriptional activity of cccDNA.
- **Increase:**
  - marker of new infection or reactivation
- **Decrease**
  - marker of efficient T cell immunity.
“HBsAg”
Natural History
Inactive carriers

Additional tool allowing to differentiate AgHBe negative patients with normal ALT and high risk of reactivation from inactive carriers.

The combination of HBsAg < 1 000 IU/mL and HBV DNA ≤ 2 000 IU/mL allows identification of inactive carriers with 90% accuracy, 88% PPV.

As effective as one year ALT follow-up

Brunetto et al. Gastroenterology 2010;139:483
Inactive carriers

Additional tool allowing to differentiate HBsAg-negative patients with normal ALT from inactive carriers. The combination of HBsAg <1000 IU/mL and HBV DNA ≤ 2000 IU/mL allows identification of inactive carriers with 90% accuracy, 88% PPV, as effective as one year ALT follow-up.

Identification of patients with high risk of reactivation that will benefit from therapy

Brunetto et al. Gastroenterology 2010;139:483
Prediction of fibrosis severity

HBeAg positive patients included in the Phase III (710) and NEPTUNE (465) trials.

The optimal cut-off of HBsAg: 17,316 IU/ml

The optimal cut-off of HBsAg: 17,714 IU/ml

Prediction score including HBsAg ≤ vs > 17,500 IU/ml and Age < vs ≥ 30 years created to reach accuracy: 85% identifying F0-F1; 95% identifying F0-F2

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0-F1</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Phase III</td>
<td>39.5%</td>
<td>87.7%</td>
<td>78.4%</td>
<td>56.2%</td>
</tr>
<tr>
<td>Neptune</td>
<td>33.2%</td>
<td>87.1%</td>
<td>75.9%</td>
<td>51.6%</td>
</tr>
<tr>
<td>F0-F2</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Phase III</td>
<td>30.9%</td>
<td>94.8%</td>
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Martinot-Peignoux et al. J Hepatol 2013;58:1089
Marcellin et al CGH 2014 on line
Prediction of fibrosis severity

HBeAg positive patients included in the Phase III (710) and NEPTUNE (465) trials.

Genotype B (AUC=0.683)

The optimal cut-off of HBsAg: 17,316 IU/ml

Genotype C (AUC=0.633)

The optimal cut-off of HBsAg: 17,714 IU/ml

- Sensitivity | Specificity | PPV | NPV
- F0-F1
  - Phase III: 39.5% | 87.7% | 78.4% | 56.2%
  - Neptune: 33.2% | 87.1% | 75.9% | 51.6%
- F0-F2
  - Phase III: 30.9% | 94.8% | 96.8% | 21.0%
  - Neptune: 27.3% | 95.5% | 97.3% | 17.8%

Prediction score including HBsAg ≤ vs > 17,500 IU/ml and Age < vs ≥ 30 years created to reach accuracy: 85% identifying F0-F1; 95% identifying F0-F2

Validated only for genotypes B and C

Martinot-Peignoux et al. J Hepatol 2013;58:1089
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## Prediction of outcome

The role of HBsAg levels in predicting clinical outcome of HBV carriers were widely investigated by 3 Taiwanese natural history studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Phase</th>
<th>Follow-up (years)</th>
<th>Risk</th>
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<tbody>
<tr>
<td>REVEAL-HBV</td>
<td>3342</td>
<td>e⁺/e⁻</td>
<td>11,4</td>
<td>Minimal cirrhosis or HCC</td>
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<td>Lee et al.</td>
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<td>OR(95%CI) 4.06(2.24-7.36)</td>
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<td>ERADICATE-B</td>
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<td>e⁺/e⁻</td>
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<td>Tseng et al.</td>
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*Validated only for genotypes B and C*
“HBsAg”
PEG-IFN therapy
Baseline HBsAg titer

Prediction of sustained virological response

*HBV DNA <2000 IU/ml + HBeAg negativation 6 months post-treatment

**HBV DNA <2000 IU/ml 6 months post-treatment

Log IU/ml

Virological response

Non-responder

P<0.001

P<0.01

P<0.01

Marcellin et al. AASLD 2013
Piratvisuth T et al. Hepatol Int 2011
Takkenberg et al. Antiviral Therapy in Press.
On treatment kinetics

HBeAg negative patients receiving 48 weeks PEG-IFN

During therapy (Week 12)

Real life S-Collate study
Low on-treatment HBsAg levels associated with higher SVR and HBsAg loss rates

Virological Response             HBs loss            Virological Response             HBs loss
46% 15% 16% 3% 62% 34% 38% 3%

\[ \leq 1500 \text{ IU/ml} \quad > 1500 \text{ IU/ml} \]

HBeAg positive

HBeAg negative

Marcellin et al. APASL 2013
When: end of therapy

HBeAg negative genotype D patients
End of treatment HBsAg level predictive of SVR and HBs loss

- 80%* Sustained virological response
- 36%* HBsAg titer
- 23%
- 17%
- 0%

End of therapy HBsAg titer:
- <10 IU/ml
- 10-100 IU/ml
- 100-1000 IU/ml
- 1000-5000 IU/ml
- >5000 IU/ml

* At year 3 post-treatment HBsAg: <10 IU/ml 52% HBs loss; >10 IU/ml ≤ 2% AgHBs loss

Conclusion PEG-IFN therapy

- Low baseline HBsAg level associated with response in both HBeAg positive-and-negative patients.

- Early HBsAg decline and level < 1,500 IU/ml at week 12 associated with probability of sustained virologic response and HBs loss.
  
  - Weeks 12 stopping rules: treatment should be discontinued in the absence of any HBs decline combined with HBV DNA decline < 2log (NPVS 80-100%).
“HBsAg”
Oral therapy
Baseline HBsAg titer

Prediction of virological response and HBsAg loss

Virological response

HBsAg loss

- Absence HBsAg loss
- HBsAg loss

p<0.001

Lee ML. et al. Hepatology 2011
Seto WK. et al. J Hepatol 2013 and Hepatology 2013
On treatment kinetics

HBsAg levels can help identify patients able to stop therapy

<table>
<thead>
<tr>
<th>HBsAg decline patterns during therapy</th>
<th>Rapid decline associated with HBsAg clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>Decline year 1</td>
</tr>
<tr>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Rapid &gt; 1 log</td>
</tr>
<tr>
<td>12</td>
<td>Slow &lt; 1 log</td>
</tr>
<tr>
<td>24</td>
<td>Steady</td>
</tr>
<tr>
<td>36</td>
<td></td>
</tr>
</tbody>
</table>

Patients with rapid decline who clear HBsAg may be able to stop therapy

During therapy

HBeAg positive patients receiving ADV and/or TDF (103 study)
Prediction of HBs loss

<table>
<thead>
<tr>
<th></th>
<th>Week 12</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 log UI/ml</td>
<td>PPV</td>
<td>35%</td>
</tr>
<tr>
<td>&lt; 1 log UI/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Marcellin et al. J Hepatol 2014;61:1228
## Post-treatment outcome

### HBsAg levels at treatment cessation predict HBV relapse and HBs loss

<table>
<thead>
<tr>
<th>Study</th>
<th>On treatment decline</th>
<th>End of treatment</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al. AVT 2011</td>
<td>≥ 2 log IU/ml</td>
<td>≤ 2 log IU/ml</td>
<td>PPV 100%</td>
</tr>
<tr>
<td></td>
<td>≤ 1 log IU/ml</td>
<td>&gt; 2 log IU/ml</td>
<td>NPV 100%</td>
</tr>
<tr>
<td>Cai et al. JCV 2010</td>
<td>≥ 1 log IU/ml</td>
<td>≤ 2 log IU/ml</td>
<td>PPV 79%</td>
</tr>
<tr>
<td></td>
<td>&lt; 1 log IU/ml</td>
<td>&gt; 2 log IU/ml</td>
<td>NPV 86%</td>
</tr>
<tr>
<td>Liang et al. APT 2011</td>
<td>≤ 2 log IU/ml</td>
<td></td>
<td>PPV 90%</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 log IU/ml</td>
<td></td>
<td>NPV 70%</td>
</tr>
</tbody>
</table>

### Figure A: Cumulative incidence of HBsAg loss

- HBsAg <120 IU/ml
- HBsAg 120-1000 IU/ml
- HBsAg >1000 IU/ml

### Figure B: Cumulative incidence of HBsAg relapse

- HBsAg <200 IU/ml
- HBsAg 200-1000 IU/ml
- HBsAg >1000 IU/ml

### Graphs

- For HBsAg loss and relapse rates over time with different HBsAg levels.

### References

- Cai et al. JCV 2010
- Liang et al. APT 2011
- Chen CH J Hepatol 2014;61:515
“HBsAg”
Combination therapy
Combinaison or Add-on

Controlled study 740 patients
HBeAg + or – ADN VHB > 2 000 UI/ml, Changes in HBsAg levels at week 48

HBsAg steeper decrease in patients receiving the combinaison TDF plus PEG-IFN

Marcellin P, France, AASLD 2014, Abs. 193
Conclusion oral therapy

- **HBeAg positive patients**
  Low baseline HBsAg level, a rapid decrease (>1 log) associated with higher chance of HBs loss.

- **HBeAg negative patients**
  Low end of treatment levels (< 100-500 IU/ml) associated with higher probability of sustained virologic response and HBs loss.
HBsAg quantification can complement HBV DNA to optimize the management of chronic hepatitis B patients.

More data are needed, especially studies from western countries, to confirm these findings and the role of HBV genotypes.

There is needs for better definition of HBsAg decline and indentified time points with best predictive fit for response and likelihood of HBs loss.
Take home message

✓ Correlates with cccDNA in liver tissue
✓ Reflects immune control and clinical stages
✓ Identifies true inactive carriers
✓ Discriminates moderate from severe fibrosis
✓ Predictor of cirrhosis and HCC development
✓ PEG-IFN: early prediction of non-response
✓ NAs: allows treatment discontinuation?
Take home message

HBsAg quantification in clinical setting:

✓ Correlates with cccDNA in liver tissue
✓ Reflects immune control and clinical stages
✓ Identifies true inactive carriers
✓ Discriminates moderate from advanced fibrosis
✓ Predictor of cirrhosis and HCC development

PEG-IFN: early prediction of non-response

NAs: allows treatment discontinuation?
References: HBsAg quantification to monitor patients


3. Martcellin et al. CGH 2015 on line


8. Wursthorn et al. Hepatology 2010;52:1611
