New HBV Biomarkers

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COI Disclosure Information

Advisory Board

BMS, Gilead, Novartis, Abbvie, MSD

Education and Research Funding

BMS, Gilead, Novartis, Abbvie, Sanofi Aventis
Scope

• Do we need more biomarkers in HBV?
• Quick Review of HBV Virology
• Some new and not so new biomarkers
  • qHBeAg and qHBsAg
  • HBcr Ag
  • HBV RNA
  • Total anti HBc levels
• Personalised management of Hep B
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• Do we need more biomarkers in HBV?
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• Personalised management of Hep B
Natural History and Treatment of CHB

- HBeAg +
- ALT elevated
- DNA >20000 IU/ml

- Immune Tolerant
- Immune Clearance (HBeAg + Chr Hepatitis)
- Low/Non-replicative
- Reactivation (HBeAg - Chr Hepatitis)

- HBV DNA
- ALT

- Fibrosis → cirrhosis
- HCC

HBeAg +
ALT elevated
DNA >20000 IU/ml

HBeAg -
ALT elevated
DNA >2000 IU/ml
Treatment Target for CHB

- Spontaneous eAg seroconversion
- sAg loss
- Treated - eAg seroconversion
- sAg loss
Outcomes of CHB

- Spontaneous eAg seroconversion
- Treated - eAg seroconversion

- sAg loss
- sAg loss

- Fibrosis $\rightarrow$ cirrhosis
- HCC
Predicting Natural History and Risk Stratification

Viral Kinetics

- Intrahepatic cccDNA
  - transcription ➔
  - DNA replication

Immune System

Natural hx- What is the dynamic tempo of CHB in individual patient?
Treatement – who to treat, how long to treat, can we stop?
Quick Review of HBV Virology

Adapted from Hu et al, Ann Rep Med Chem 2013
Quick Review of HBV Virology
Scope

• Do we need more biomarkers in HBV?
• Quick Review of HBV Virology
• Some new and old markers on the block
  • qHBeAg and qHBsAg
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• Personalised management of Hep B v3.0
qHBeAg for predicting outcomes of CHB Rx

**eAg seroconversion in Peg Rx**

**eAg seroconversion in ETV**

*Fried, Hepatology 2008*

Multivariate analysis of HBV DNA, qHBsAg & qHBeAg At baseline, 3m, 6m, 9m & 12m shows:
- Only qHBeAg at 12 m predicts HBeAg seroconversion with cutoff level 0.62 log_{10} PEIU/ml
- Absolute level of qHBeAg was superior to log_{10} decline in qHBeAg

*Shin, J Viral Hepatitis 2012*
Quantitative HBsAg- Predicting HBsAg loss with HBeAg seroconversion

n=775 HBeAg seroconverters (45% on antiviral therapy)

- HBsAg loss
  - HBsAg <750 IU/ml: 33%
  - HBsAg 751-3,750 IU/ml: 8.6%
  - HBsAg >3,750 IU/ml: 6.2%

AUROC=0.742

HBsAg level 1y post HBeAg seroconversion for predicting HBsAg loss
Serum HBsAg level reflects the cccDNA transcription or mRNA translation, but also host immune control over HBV infection.

Natural History
HBsAg 1 Year after HBeAg-seroconversion predict HBsAg loss

HBeAg-negative carriers with a low viral load (<2,000 IU/ ML)
qHBsAg for predicting outcomes of CHB

Natural History
HBeAg-negative carriers with a low viral load (<2,000 IU/ML)

Multivariate analysis revealed that HBsAg level $\geq 1,000$ IU/mL was an independent risk factor for HCC development

Tseng Gastroenterology 2012
Quantitative HBsAg- Predicting HBsAg loss

HBsAg decline of $\geq 1$ log10 IU/ml at week 24 predicted HBsAg loss (HR = 13.7, 95% CI 5.6–33.7; p <0.0001)
Baseline HBsAg predict response to Peg-IFN-α2b therapy in HBeAg-positive Chinese CH-B

Virologic response at 48 weeks of PegIFN therapy (%)

- >20,000: 18 (16.7%)
- 1,500-20,000: 26 (42.3%)
- <1,500: 63.6

Baseline HBsAg levels (IU/mL)

Virologic response: HBV DNA < 1,000 IU/mL and HBeAg seroconversion

### Predictive Tool for stopping Peg

<table>
<thead>
<tr>
<th><strong>HBeAg-negative patients</strong></th>
<th><strong>HBeAg-positive patients</strong></th>
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<tbody>
<tr>
<td><strong>Week 12</strong></td>
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<tr>
<td>Stop if no HBsAg decline &amp;</td>
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</tr>
<tr>
<td>HBV DNA decline &lt;2log</td>
<td>(GT A+D) or if HBV DNA</td>
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<tr>
<td>(GT D)</td>
<td>&gt;20 000 IU/ml (GT B+D)</td>
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<td><em>(PEGBeLiver + PEG2a registration trial, n=160)</em></td>
<td><em>(PEG2a registration trials, n=803)</em></td>
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<td>NPV 95%-100%</td>
<td>NPV 99%</td>
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*Rijckborst et al., J Hepatol 2012; Sonneveld et al., Hepatology 2014*
Antigenic activity combining
- Denatured HBeAg
- Core related Ag - p22cr
- HBcAg

- Correlated with HBV DNA levels as part of viral replication
- More closely reflect intrahepatic cccDNA translation activity
- Commercial test with wide detection range available -- chemiluminiscence enzyme
- Possible to detect when DNA is undetectable
- Positive even in anti HBc ab + patients who have lost HBsAg

Kimura et al., J Clin Microbiology 2002
Correlation of HBcr Ag with HBV viral activity

Kimura J Clin Microbiology 2002
Correlation of HBcr Ag with HBs disease

- HBcrAg levels of IT, IC, ENQ, and ENH were 9.30 log U/mL, 8.80 log U/mL, 3.00 log U/mL, and 5.10 log U/mL, respectively (p < 0.0001)

- HBcrAg at cutoff values of 4.15 log U/mL discriminated between the ENQ and ENH phases. AUROC 0.931, sensitivity: 87.93% and specificity of 84.00%

Gou Clin Lab 2017
HBcrAg predicts hepatocellular carcinoma in non-treated HBV patients

78/1031 CHB developed HCC after 10.7 years. HBcrAg >2.9 log U/ml (hazard ratio (HR), 5.05; 95% confidence interval (CI), 2.40–10.63) and BCP mutation (HR, 28.85; 95% CI, 4.00–208.20) were independently associated with the incidence of HCC. Time-dependent ROC analysis showed that HBcrAg was superior to HBV DNA.

*Tada et al., J Hepatology 2016*
HBcrAg predicts cirrhosis in non-treated HBV patients

83 /1031 untreated CHB developed cirrhosis after 10.7 years. HBsAg and HBcrAg are independently associated with progression to cirrhosis.

HBsAg <3.0 log IU/ml (HR, 0.53; 95% confidence interval (CI), 0.30–0.94)

HBcrAg ≥3.7 log U/ml (HR, 3.28; 95% CI, 1.60–6.75)

Tada et al., JGH 2017
HBcrAg as predictor of treatment outcome

Allows monitoring as surrogate of cccDNA even when HBV DNA is undetectable due to Rx

Predict risks of flare if antiviral is stopped

Potential use to decide duration for Rx of oral antiviral

Matsumoto et al., Hepatology Research 2002;
HBV RNA in serum

HBV RNA is found in the serum and is found to be extruded into the serum as virus like particle.

Patients taking NA would see a increase in HBV RNA as viral replication is blocked but cccDNA transcription occur

HBV RNA is potentially useful in predicting cccDNA activity for patients on NA and when deciding whether to stop NA
Drop in HBV RNA was independently associated with response to Peg-IFN and adefovir in HBe Ag–negative patients, a lower baseline plasma HBV RNA level predicted sustained complete response. (odds ratio, 0.44; P = .019).

Hep Bc Ig Total

Double antigen sandwich immunoassay
marker of immune response

N=800 patients NA or Peg-INF. baseline anti-HBc level was the best independent predictor for HBeAg seroconversion (OR 2.178; 95% CI 1.577 to 3.009; p<0.001).

Fan. GUT 2016
Personalised Treatment of CHB

1. Patients who do not fulfil criteria for HBV treatment may not be inactive carriers and can develop liver complications such as cirrhosis and HCC.

2. Better risk profiling with markers looking at cccDNA activity and immune response will allow identification of CHB patients at risk
   a. HBV DNA kinetics
   b. Quantitative HBsAg, HBcrAg

3. Biomarkers may better advise success and futility of treatment and thus guide decisions to continue or stop therapy. e.g. HBsAg, HBcrAg, HBV RNA, anti HBcIg
Thank You