Utility of serum biomarkers to follow clinical phases and treatment of CHB: A clinical perspective

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GRANTS
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The ideal biomarker...

- Predictive (visible early, and indicative of, clinical outcome)
- High specificity
- High sensitivity, also correlation with severity
- Reflective of durable response
- High reproducibility
- Non-invasive/accessible
- Rapid/simple
- Inexpensive
Potential New Viral and Immunologic Biomarkers

**Viral**
- Quantitative hepatitis B surface antigen (HBsAg)
- Hepatitis B core-related antigen (HBcrAg)
- Pregenomic hepatitis B virus RNA (HBV RNA)
- (Quantitative) cccDNA in liver/blood
- HBsAg epitope mapping

**Immunologic**
- HBV-specific T & B-cell response
- T-lymphocyte markers
- Expression of inhibitory molecules (PD-1, Tim-4, CTLA4)
- Quantitative anti-HBs
- Anti-HBc (IgM/total)
Biomarkers in Current Clinical Practice
Natural History of CHB in 2020

Treatment indicated

- Immune tolerance
  - HBeAg

- Immune active
  - HBeAg or anti-HBe

- Immune control
  - Anti-HBe

HBV DNA
$log_{10}$ IU/ml

HBsAg
$log_{10}$ IU/ml

ALT (U/L)

HBsAg
How useful is Serum HBsAg Quantification?

- HBsAg loss associated with better outcome: less cirrhosis, HCC and mortality
- Low HBsAg (<1000) good marker to distinguish between true inactive and active HBeAg-neg disease in natural history
- Low HBsAg (<10-100) best predictor in prevention of relapse after stopping NA
- Good predictor for PEG-IFN response: Response guided therapy
- HBsAg loss very stable endpoint as off-treatment sustained response for both PEG-IFN and NA
- HBsAg loss used for functional cure in new treatment trials
- In HBeAg negatives HBsAg production largely driven by integrated HBV DNA and not by cccDNA

HBsAg: HCC Prediction

- Higher HBsAg levels independently associated with HCC development (Lee 2013)
- Among patients with low-medium viral load, higher HBsAg levels independently predict HCC development; enhanced performance when combined with HBV DNA (Tseng 2012, Tseng 2013)
- However, excluded from most HCC prediction models; only incorporated into “REACH-B” model (Voulgaris 2020)
X-targeting siRNA Therapy VIR-2218-1001 Phase 2 Study Results
HBsAg change from baseline

*Follow-up only available for all placebo patients through Week 16

HBsAg <100 IU/mL at Week
- 24: 33%
- 24: 44%
- 24: 50%
- 24: 50%

Gane E et al., EASL 2020
HBsAg Reduction Leading to ALT Flare from ASO Treatment in 3 Patients on NA Therapy

- ALT flare initiates as HBsAg is being depleted, flares were asymptomatic and self-resolved

Patient A: Maximum ALT increase of ≥3 × ULN and >1.0 log_{10} HBsAg reduction

Patient B: Maximum ALT increase of ≥3 × ULN and >1.0 log_{10} HBsAg reduction

Patient C: Maximum ALT increase of ≥5 × ULN and >1.0 log_{10} HBsAg reduction

MF Yuen et al EASL 2020
HBcrAg
Hepatitis B core related antigen (HBcrAg)

• Combined measure of 3 viral proteins transcribed from the precore/core gene of the HBV genome ¹:
  – HBcAg, HBeAg, 22-kDa precore protein (p22cr)
• HBcrAg is a surrogate marker of both intrahepatic cccDNA and its transcriptional activity²,³
• Can be useful in the evaluation of new antiviral therapies aiming at a functional cure of HBV infection either by targeting directly or indirectly the intrahepatic cccDNA pool
• Associated with response to current antiviral therapy for HBeAg-positive CHB⁴
• Sensitivity needs to be improved: Lower limit of quant 3 log U/mL- Upper limit of quantitation is 6.8 log U/mL Chemiluminescent Enzyme Immunoassay (Fujirebio).

HBcrAg: Following Natural History

- HBcrAg levels higher in HBeAg-positive vs -negative phase (Testoni 2019, Wong 2016, Maasoumy 2015)

- Correlates with intrahepatic cccDNA levels and transcriptional activity – better in HBeAg-positive phase (Testoni 2019)

- Potential use in distinguishing between inactive carriers and those with HBeAg-negative active disease (Maasoumy 2015)

- Limited by:
  - sensitivity of assay
  - PC/BCP mutants

Mak et al., *Aliment Pharmacol Ther* 2018
HBcrAg: HCC Prediction

- High baseline levels associated with higher risk of HCC development treatment-naïve patients; HBcrAg superior to other biomarkers in predictive power (Tada 2016, Tseng 2019)
- Persistently high on-treatment HBcrAg levels independently associated with higher risk of HCC in NA-treated patients (Hosaka 2019)
- Detectable levels after NA for >2 years an independent risk factor for HCC (Honda 2016)

Tseng et al., *Gastroenterology* 2019
HBV RNA
HBV RNA: Following Natural History

- Serum HBV RNA – primarily full-length, encapsidated pregenomic RNA (Wang 2016, Anderson 2020)
- Its levels highest in immune-tolerant, lowest in inactive carrier phase (Wang 2018)
Factors influencing serum HBV RNA

Van Campenhout MJH et al. Hepatology 2018
Serum HBV RNA as a Clinical Marker

- Usefulness in prognostication of natural history of CHB is unclear. Paucity of data on its predictability for HCC development

- Measurement of serum HBV RNA can be used for monitoring viral dynamics in HBV DNA negative patients under treatment

- Pretreatment HBV RNA is associated with response to nucleos(t)ide analogues (NA) and peginterferon alpha (PEG-IFN) alone

- Useful to predict durable response after stopping NA: undetectable HBVRNA together with HBsAg<10

- HBV RNA measurements helps monitoring the effectiveness of drugs aiming to affect cccDNA transcription and/or pgRNA stability (CAM and siRNA)

- Sensitivity should be improved. Undetectable in many (>50%) HBeAg neg patients on long-term NA therapy. Lower limit of quant 1.65 log IU/mL (Abbott Diagnostics)
How do the HBV biomarkers compare?
Different biomarkers perform differently for different drugs
JNJNA plus JNJ 6379 (CAM): HBV DNA and HBV RNA Dynamics

Janssen HL, et al. EASL 2020
GLS4 (CAM) plus ETV in HBeAg pos Patients (phase 2)

- GLS4: Class I CpAM
- HBeAg+ patients
- Two cohorts:
  - Treatment-naive (TN), n=125
  - Virologically suppressed (VS) on ETV, n=125
- Both cohorts:
  - 4:1 GLS4 120 mg/ Ritonavir 100 mg TID + ETV 0.5 mg QD vs ETV alone

Zhang M et al. EASL 2020
Different serum markers in predicting treatment response to Peg-IFNa-2a in CHB

HBeAg-positive patients

- HBcrAg associated with treatment response for NA +/- peg-IFN in both HBeAg pos and HBeAg neg CHB.
- HBcrAg was however not superior to HBsAg in predicting response to therapy

Conclusions

• HBeAg, quant HBsAg and HBVDNA will likely remain to be the most important biomarkers used in natural history and treatment endpoints because they are best validated to reflect outcome
• Biomarkers have a different importance in different disease phases (HBe pos vs neg), HBV genotypes and for different treatment modalities
• HBV RNA and HBcrAg are related to outcome of current and new therapies, but may not better predict treatment outcome than quant HBsAg
• HBV RNA and HBcrAg tests need to be well validated and their sensitivity needs to be optimized
• New biomarkers can help to dissect mechanism of action of new drugs
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