Use of Biomarkers to Monitor HBV therapy

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Outline

Role of alternative HBV biomarkers

1. Quantification of HBV cccDNA
2. Quantification of circulating HBeAg
3. Quantification of circulating HBsAg

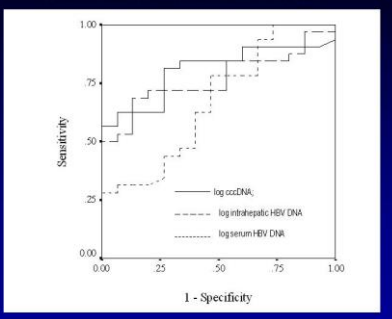
Context: Predictors of antiviral response

HBV cccDNA Levels as a Predictor of Sustained Virological Response

- IFN & LMV combination vs LMV monotherapy (patients = 47)
- Evaluated serum HBV load, intrahepatic HBV DNA and cccDNA as predictors of response

Sung et al (2005) Gastroenterology 128:1890

ROC curve of log serum HBV DNA, intrahepatic DNA and cccDNA for SVR



cccDNA levels give the highest predictive value for SVR

HBV cccDNA as a Predictor of Response

- Short term treatment can reduce but does not eliminate HBV cccDNA
- Low levels at baseline may predict a better antiviral response
- Low end-of-treatment levels can predict a durable viral response

BUT

- Assay is not standardized
- Requirement for multiple biopsies
- Alternatives to biopsies now being used (TE, Fibroscan, Fibrotest, APRI, ELF)
- Fine needle aspirates?

- Need an alternative marker that correlates with HBV cccDNA

Clinical Testing for Quantitative HBeAg

- A role for quantitative HBeAg titre in predicting treatment outcome has been proposed:

1) Pegylated-interferon therapy:

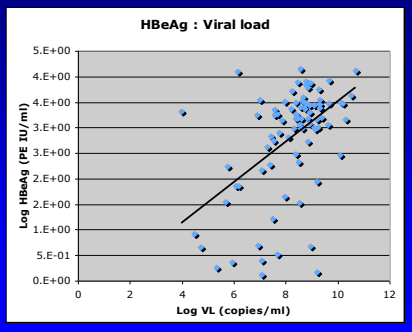
– HBeAg seroconversion

- Baseline HBeAg titre < 31 PE IU/ml – PPV for seroconversion = 51%

- 24 week HBeAg titre > 100 PE IU/ml – NPV for seroconversion = 96%

(Fried, Hepatology, 2008)

HBeAg correlated weakly with serum HBV DNA

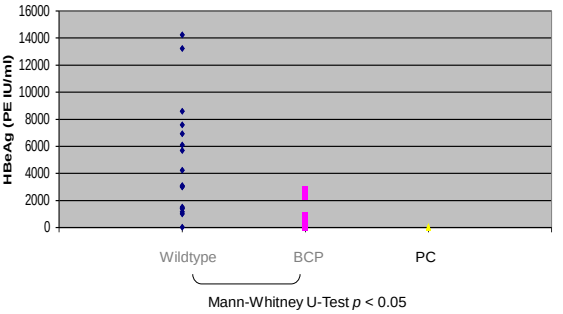


r = 0.35
p = 0.001

Thompson et al 2010 Hepatol 51: 1933

HBV Variants and HBeAg Titre *in vivo*

PC/BCP variants reduce HBeAg titre



Mann-Whitney U-Test $p < 0.05$

Conclusion – HBeAg titre

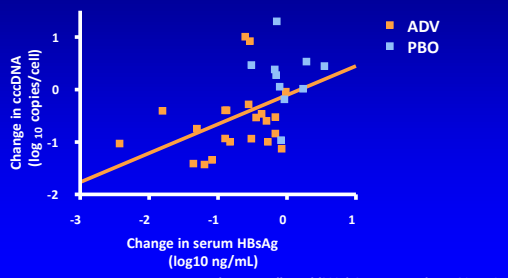
- HBeAg titres were log-normal distributed and only modestly correlated with viral load and cccDNA
- This was due to the presence of BCP/PC variants reducing HBeAg titre independent of viral load.
- With a WT HBV infection qHBeAg <31 PE IU/mL may be predictive of response but not in the setting of emerging BCP/PC variants
- BCP/PC sequencing is required when evaluating the utility of HBeAg titres in predicting treatment outcome

Thompson et al 2010 Hepatol 51: 1933

HBsAg Seroclearance as an Endpoint

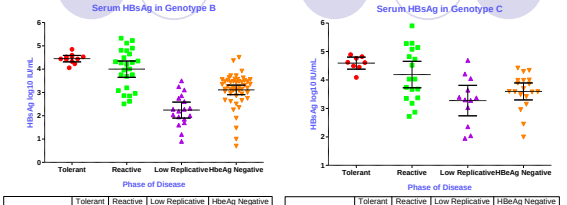
- HBsAg seroclearance indicates successful immunological control of HBV infection
  - Associated with favourable long-term clinical outcomes
  - Can be induced by IFN-based therapy
  - Less commonly achieved by treatment with nucleos(t)ide analogues
- Can HBsAg quantification provide a predictive value?

Changes in Serum HBsAg levels are Correlated with Changes in HBV cccDNA Titre



Werle-Lapostelle et al (2004) Gastroenterology 126:1750

HBsAg Titre by Genotype



	Tolerant	Reactive	Low Replicative	HBeAg Negative
Number of values	11	25	18	49
25% Percentile	4.330	3.140	1.813	2.900
Median	4.440	4.210	2.240	3.240
75% Percentile	4.540	4.720	2.778	3.525

	Tolerant	Reactive	Low Replicative	HBeAg Negative
Number of values	8	18	12	19
25% Percentile	4.460	3.365	2.528	3.420
Median	4.615	4.030	3.335	3.600
75% Percentile	4.805	5.095	3.948	3.990

Nguyen et al 2010 J Hepatol 52: 508

Role of Quantitative HBsAg

Treatment with PEG IFN +/- LMV

	Week 12 HBsAg on PEG IFN alfa 2a ± LMV	HBV DNA ≤ 10000 copies/ml		HBV DNA ≤ 400 copies/ml		HBsAg loss	
		6 months	4 years	6 months	4 years	6 months	4 years
HBeAg-negative	≤ 1500 IU/mL	59%	39%	39%	31%	**7%**	**23%**
	> 1500 IU/mL	34%	12%	9%	8%	2%	4%

Marcellin, P. et al 2008. AASLD

Role of Quantitative HBsAg – HBeAg positive CHB

Treatment with PEG IFN +/- LMV

		End of Treatment (W48)		
	Week 12 HBsAg on PEG IFN alfa 2a ± Lamivudine therapy	HBV DNA ≤ 10,000 copies/ml	HBV DNA ≤ 400 copies/ml	HBsAg loss
HBeAg-positive	≤ 1500 IU/mL	46.8%	31.2%	**10.1%**
	1501 – 20,000 IU/mL	22.6%	11.1%	1.8%
	> 20,000 IU/mL	8.2%	4.1%	3.3%

Lau, G. et al 2008. AASLD

Serum HBV RNA

- 50 HBeAg-positive patients on NA therapy
- 15 achieved HBeAg seroconversion
- Had the strongest decline in serum HBV RNA

Van Bommel et al 2014 Hepatol

- 52 patients on NA therapy – HBV RNA at 12W & 24W
- 21/52 detectable HBV RNA at baseline
- Lowest HBV RNA at W12 were best responders

Huang et al 2014 Antiviral Ther

Update – IFN –HBeAg-positive CHB

- qHBsAg < 300 IU/mL at W24 correlates with SVR
  - *Chan et al 2010 Aliment Pharmacol Ther 32: 1323*
- qHBsAg <1500 IU/mL at W12 corresponds to 57% PPV for HBeAg seroconversion
  - *Lau & Marcellin 2009 J Hepatol 50: 333*
- qHBsAg > 20,000 IU/mL at W12 100% NPV for anti-HBs seroconversion
  - *Liaw et al 2011 Hepatology 54:1591*

Update – IFN –HBeAg-negative CHB

- qHBsAg >0.5 log at W12 leads to ETR in 90%
  - *Moucari et al 2009 Hepatol 49: 1151*
- No or little decline in qHBsAg and <2 log decline of HBV DNA shows a NPV of 100%
  - *Rijckborst et al 2010 Hepatol 52: 454*
- qHBsAg <1000 IU/mL & HBV DNA <2000 IU/mL
- Corresponds to 88% PPV for discriminating low replicative phase from HBeAg-negative phase
  - *Brunetto et al 2010 Gastro 139: 483*

Update – NAs and qHBsAg

- qHBsAg decline > 1 log at W48 correlates with HBsAg loss
  - *Chan et al 2011 Antiviral Ther 16: 1249*
- qHBsAg decline >0.5 log after 2 years of HBV DNA suppression correlates with HBsAg loss
  - *Jaroszewicz et al Antiviral Ther 16: 915*
- qHBsAg <100 IU/mL predict sustained response 2 years after EOT
  - *Cai et al 2010 J Clin Virol 48: 22.*

Role of qHBsAg in CHB Management

- With HBV DNA can define low replicative stage
- May further define other phases – I/T > I/C?
- IFN – early identification of non-responders
  - identification of responders needs further work
- NA – HBsAg decline can be associated with future seroclearance
  - May be useful in defining stop points of therapy

Confounders

- Genotype
- PreS1 mutations