Treating Immune-tolerant CHB: Factors Associated with Significant Decline in HBeAg and HBsAg Levels

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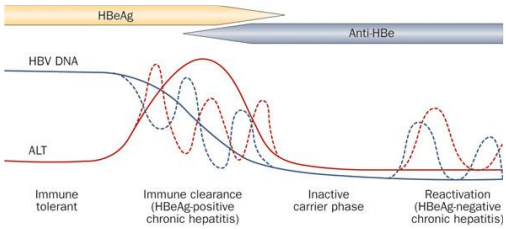
Immune-tolerant Phase of CHB



Kwon *et al* Nat Rev Gastroenterol Hepatol. 2011

Treatment

- Immune-tolerant (IT) patients are not typically recommended for treatment
  - Concerns over poor treatment response
  - Low levels of disease progression observed
- However early treatment may be associated with a reduction the risk of cirrhosis and HCC development

EASL, AASLD, APASL Guidelines; Zoulim F *et al* Gut. 2012

Gilead GS-US-203-0101 Trial

- The GS-US -203-0101 trial evaluated the efficacy of antiviral therapy (TDF and FTC/TDF) over 192 weeks for 126 patients in the IT phase of CHB.
- 70% achieved viral suppression. However low rates of HBeAg loss (4%) and no HBsAg loss were observed.
- The aim of this follow up study is to undertake a detailed virological characterisation:
  - at baseline to shed light on the IT phase of CHB
  - on treatment HBsAg and HBeAg response to determine predictors of positive treatment outcomes (> 1 $\log_{10}$ decline)

Chan HL *et al* Gastroenterology. 2014

Methods

Patient Population	• Patients from the GS-US-203-0101 trial (n=126) were eligible • Inclusion criteria included treatment naïve, HBeAg positive, high HBV DNA (>7.3$\log_{10}$IU/ml) and ALT<ULN
HBV markers	• HBV DNA (Roche COBAS TaqMan)and HBsAg (Abbott Architect) testing at CROs (n=1149) • HBeAg (Roche ELECSYS) testing at VIDRL (n=1149)
HBV sequencing	• Full genome population sequencing at VIDRL (n=123 baseline, n=40 viremic at EOT or early EOT) • Mutational analysis was carried out against genotype specific consensus sequence
Analysis	• Performed on genotype B and C infected individuals where complete data were available (n=113 baseline, n=93 EOT)

Baseline Profile

Patient characteristics of this IT cohort	**(n=113)**
Age (yrs), median [IQR]	32 [26-40]
Male, n (%)	54 (48)
Asian, n (%)	108 (86)
BMI (kg/m^2), median [IQR]	22 [21-25]
ALT (IU/mL), median [IQR]	25 [20-32]
HBsAg ($\log_{10}$ IU/mL), median [IQR]	4.8 [4.6-5.0]
HBeAg ($\log_{10}$ PE IU/mL), median [IQR]	3.5 [3.3-3.7]
HBV DNA ($\log_{10}$ IU/mL), median [IQR]	8.4 [8.2-8.6]
HBV Genotype B, n (%)	63 (56)
HBV Genotype C, n (%)	50 (44)

Baseline Mutations

- HCC / disease progression
  - Basal Core Promoter (BCP) (13%)
  - PreS (10%)
- Immune evasion
  - BCP (13%)
  - PreS (10%)
  - HBsAg G145R (3%)
  - Precore (2%)
  - Core deletions (2%)
- Drug Resistance mutations
  - None (0%)

Chotiyaputta W *et al* Nat Rev Gastroenterol Hepatol 2009; Locarnini S *et al* Antivir Ther. 2010; Pollicino T *et al* J Hepatol. 2014

Baseline HBsAg

- Median HBsAg level in IT was significantly higher than in comparator immune-clearance cohort
  - 60 000 IU/ml vs 16 000 IU/ml (p<0.001)
- Lower baseline HBsAg within this IT cohort was independently associated with:-
  - Lower viral load (p<0.001)
  - Gender F>M (p=0.001)
  - Younger age (p=0.007)
  - Genotype C>B (p=0.008)
  - Immune evasion mutations (p=0.001)

Bayliss J *et al* poster P672 EASL 2014

Baseline HBeAg

- Median HBeAg level in IT was significantly higher than in comparator immune-clearance cohort
  - 3500 PE IU/ml vs 1000 PE IU/ml (p<0.001)
- Lower baseline HBeAg within this IT cohort was independently associated with:-
  - Lower viral load (p=0.03)
  - Genotype B>C (p=0.02)
  - Immune evasion mutations (p=0.002)

Bayliss J *et al* poster P672 EASL 2014

Baseline summary

- Clinically important HBV variants, including those linked to disease progression, were detected in a substantial minority of immune tolerant individuals
- Individuals harbouring immune evasion variants had lower baseline levels of HBsAg and HBeAg
  - These mutations are suggestive of host immune pressure and could be predicting a transition towards immune clearance disease

On-treatment responses

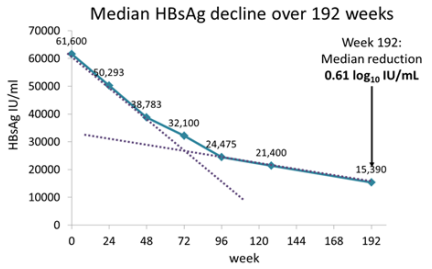
Week 192 (end-of-treatment) response	**n = 93**
HBV DNA decline > 6 $\log_{10}$ IU/mL	85 (91%)
HBV DNA < 29 IU/mL	65 (70%)
HBsAg decline > 1 $\log_{10}$ IU/mL	18 (19%)
HBsAg < 1000 IU/mL	8 (9%)
HBsAg loss	0 (0%)
HBeAg decline > 1 $\log_{10}$ IU/mL	28 (30%)
HBeAg < 100 PEIU/mL	21 (23%)
HBeAg loss	3 (3%)

HBV DNA on-treatment

- HBV DNA suppression after 192 weeks of treatment was independently associated with:-
  - Treatment (FTC/TDF >TDF) and gender (F>M), as reported previously
  - No baseline virological factors were predictors of EOT response
- Antiviral resistance mutations
  - On-treatment samples from still viremic patients were sequenced by population sequencing and next generation deep sequencing
  - No known antiviral resistance mutations emerged on treatment

Chan HL *et al* Gastroenterology. 2014

HBsAg on-treatment

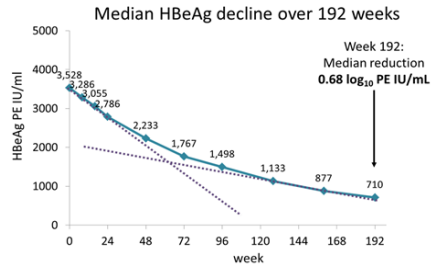


HBsAg on-treatment

- Decline of HBsAg >1log$_{10}$ over 192 weeks of treatment was seen in 19% of individuals.
- This was independently associated with:-

Odds Ratio Estimates		
Effect	OR	P-value
Lower Baseline HBsAg level	7.14	0.02
Genotype B	3.92	0.02
Higher Baseline HBV DNA	10.8	0.04
Higher Baseline ALT	1.06	0.09

HBeAg on-treatment

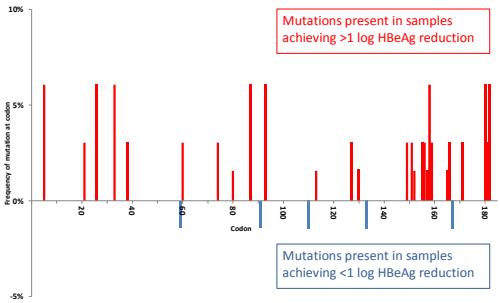


HBeAg on-treatment

- Decline of HBeAg >1log$_{10}$ over 192 weeks of treatment was seen in 30% of individuals.
- This was independently associated with:-

Odds Ratio Estimates		
Effect	OR	P-value
Lower Baseline HBsAg level	25.0	0.002
Genotype B	5.00	0.02
Higher Baseline ALT level	1.11	0.007
Mutations across the core protein	5.41	0.009

HBeAg – Core protein Analysis



On-treatment summary

- Long-term potent NA therapy is associated with significant decline of HBeAg and HBsAg of in 30% and 19% of immune tolerant persons respectively.
- Evidence of immune activity / immune clearance transition (lower HBsAg, higher ALT, increased mutations in core protein) is associated with this positive treatment outcome

Conclusions

- Monitoring HBsAg and HBeAg alongside HBV DNA gives a more accurate picture of treatment response
- Patients in the 'window period' at the end of the IT phase (with immune activity and virological response but before clinical symptoms) had more significant declines in HBeAg and HBsAg levels
- These individuals could further benefit from add-on immunomodulatory therapy; a strategy that warrants further clinical evaluation.

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