Long-term outcome in Caucasian patients with hepatitis B e antigen negative chronic infection: an observational cohort study

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1 INTRODUCTION

- Patients with hepatitis B e antigen (HBeAg)-negative chronic infection, also called inactive carriers, have normal transaminases and a low viral load
- They usually have hepatitis B virus (HBV) DNA levels < 2,000 IU/mL[1-3]
- Some patients in this phase, however, may have **HBV DNA levels between 2,000 and 20,000 IU/mL**[1]
- The natural history of this subgroup in Caucasian patients is not well-characterized

2 AIM

- To explore **factors predicting outcome during long-term follow-up**

3 METHOD

- **Multicentre retrospective cohort study**
- The study identified all consecutive chronic HBV patients of the participating centres between 1 January 1986 and 31 July 2018 who fulfilled the following **inclusion criteria**:
  - Caucasian race
  - ≥ 1 year follow-up
  - HBeAg negative and anti-HBe positive
  - HBV DNA < 20,000 IU/mL
  - persistently normal ALT levels over at least a period of 12 months
- **Exclusion criteria**:
  - Previously treated with HBV antiviral agents
  - Advanced liver disease at presentation
  - Co-infection, alcohol abuse, evidence of other coexisting liver disease
- **Primary outcome**: development of chronic active hepatitis B, i.e. ALT > 2 x ULN and HBV DNA > 2,000 IU/mL whether or not with HBeAg reversion[1-3]
- Estimates on the rate of active hepatitis B were calculated using the Kaplan Meier method

4 RESULTS

- 437 Caucasians were included (**Table 1**)
- During a mean follow-up of 12 years, 376 (86.0%) showed sustained remission, whereas 36 (8.2%) developed **chronic active hepatitis B**. Twenty-five patients (5.7%) had ALT level > 2 x ULN of unknown cause
- Out of 36 patients with active hepatitis B, 14 were considered to be the result from **immunosuppressive therapy** given for other diseases
- **Figure 1** illustrates the spontaneous progression to chronic active hepatitis B by baseline HBV DNA level in 423 Caucasian patients (i.e. after excluding those with immunosuppression-related HBV reactivation)
- The incidence of chronic active hepatitis B was significantly higher in patients with baseline HBV DNA level ≥ 2,000 IU/mL than in patients with baseline HBV DNA level < 2,000 IU/mL (p < .001)
- **Advanced liver disease, cirrhosis, hepatocellular carcinoma (HCC) and liver-related mortality** developed in 18/423 (4.3%), 6/423 (1.4%), 0/423 (0.0%) and 1/423 (0.2%) patients, respectively
- The cumulative probabilities of **advanced liver disease** were 2.3%, 4.3%, 8.6% and 17.0% at 5, 10, 15 and 20 years follow-up. Among those with HBV DNA < 2,000 IU/mL these data were 1.3%,1.8%, 3.6% and 9.2%
- **HBV DNA > 2,000 IU/mL and obesity** were independent predictors of advanced liver disease (p =.001 and p = .006)

Table 1. Baseline Characteristics of 437 Caucasian patients with HBeAg-negative chronic infection. A total of 376 individuals had sustained remission of liver inflammation, while 36 developed chronic active hepatitis B.

Characteristics	All (n=437)	Sustained remission (n=376)	Chronic active hepatitis B (n=36)	*P* Value
Baseline Age (years)	34 ± 13.6	34 ± 13.4	33 ± 12.6	.544
Gender, males (%)	220 (50.3)	188 (50.0)	17 (47.2)	.750
Obesity†, (%)	35 (8.0)	30 (8.0)	1 (2.8)	.343
Baseline ALT level (IU/mL)	24 ± 8.1	24 ± 8.3	26 ± 7.0	.127
qHBsAg level (IU/mL)‡,§	362 ± 2107.6	365 ± 1665.3	304 ± 3348.9	.779
Baseline HBV DNA, (log IU/mL)‡	2.2 ± 3.15	2.2 ± 3.09	3.3 ± 3.51	**.002**
HBV DNA quantified, (%)	268 (61.3)	231 (61.4)	26 (72.2)	.202
HBV DNA ≥ 2,000 IU/mL, (%)	91 (20.8)	67 (17.8)	20 (55.6)	**<.001**
HBV DNA ≥ 5,000 IU/mL, (%)	46 (10.5)	37 (9.8)	6 (16.7)	.247
HBV DNA ≥ 10,000 IU/mL (%)	19 (4.3)	14 (3.7)	3 (8.3)	.178

Values shown as mean ± standard deviation or as n (%)

Abbreviations: ALT: alanine aminotransferase; qHBsAg: quantification of hepatitis B surface antigen

†Obesity was defined as BMI > 30 kg/m^2

‡Mann-Whitney U nonparametric test was used instead and medians + interquartile range (IQR) were shown as appropriate

§Data on qHBsag were available in 156/437 (35.7%) patients

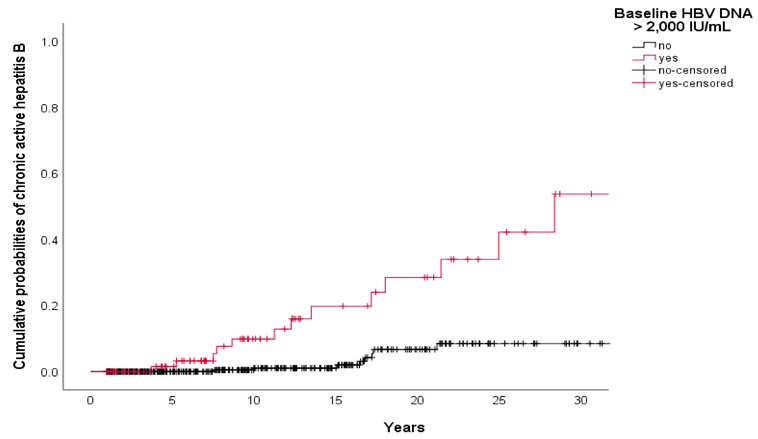

Figure 1 Cumulative probabilities of development to chronic active hepatitis B in 423 Caucasian patients with HBeAg-negative chronic infection by baseline HBV DNA level. Patients were censored on the date of last outpatient clinic visit

5 CONCLUSIONS

- In Caucasian patients with HBeAg-negative chronic infection, the **level of viremia** affects prognosis
- Patients with HBV DNA level < 2,000 IU/mL confer a favourable prognosis with **no risk of HCC**, which suggests that there is no need for intensive follow up and screening for HCC
- In contrast, patients with a HBV DNA level > 2,000 IU/mL are at risk of spontaneous development of a chronic active hepatitis and need further specialized follow up

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