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

ÖM Koc1,2, G Robaesys2,3, H Topal1, R Bielen1, D Buschots2,3, ME Gamliel, J Fevery, GH Koek2, F Nevens3
1Ziekenhuis Oost-Limburg, Genk, Belgium, 2Hasselt University, Hasselt, Belgium, 3Maastricht UMC+, Maastricht, the Netherlands; 4University Hospitals KULeuven, Leuven, Belgium, 5SUH University Hospital of the RWTH, Aachen, Germany

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
- Some patients in this phase, however, may have HBV DNA levels between 2,000 and 20,000 IU/mL
- 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
  - Advancing 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 HBeAg reversion
- 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 ($p<0.001$)
- Advanced liver disease, cirrhosis, hepatocellular carcinoma (HCC) and liver-related mortality developed in 18/423 (4.3%), 6/423 (1.4%) 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 ($p=0.001$ and $p=.006$)

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

6 ACKNOWLEDGEMENTS

This study is part of the ‘Limburg Clinical Research Program’ (LCRP), supported by the foundation Limburg Stark Mark, Province of Limburg, Flemish government, Hasselt University, Ziekenhuis Oost-Limburg and Jessa Hospital.

7 REFERENCES


8 CONTACT

Ozgur M Koc
ozgur.koc@uhasselt.be
+32.89.321519

Table 1. Baseline Characteristics of 423 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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (n=423)</th>
<th>Sustained remission (n=376)</th>
<th>Chronic active hepatitis B (n=36)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Age (years)</td>
<td>34 ± 13.6</td>
<td>34 ± 13.4</td>
<td>33 ± 12.6</td>
<td>.544</td>
</tr>
<tr>
<td>Gender, males (%)</td>
<td>220 (50.3)</td>
<td>188 (50.0)</td>
<td>17 (47.2)</td>
<td>.750</td>
</tr>
<tr>
<td>Obesity (BMI ≥ 30)</td>
<td>35 (8.0)</td>
<td>30 (8.0)</td>
<td>5 (13.9)</td>
<td>.343</td>
</tr>
<tr>
<td>Baseline ALT (IU/mL)</td>
<td>24 ± 8.1</td>
<td>24 ± 8.3</td>
<td>26 ± 7.0</td>
<td>.127</td>
</tr>
<tr>
<td>pTHBAg level (IU/mL)</td>
<td>362 ± 210</td>
<td>365 ± 166.3</td>
<td>304 ± 134.9</td>
<td>.779</td>
</tr>
<tr>
<td>Baseline HBV DNA, (log IU/mL)</td>
<td>2.2 ± 3.5</td>
<td>3.2 ± 3.0</td>
<td>3.3 ± 3.5</td>
<td>.000</td>
</tr>
<tr>
<td>HBV DNA quantifyed, (%)</td>
<td>268 (61.3)</td>
<td>231 (61.4)</td>
<td>36 (102.2)</td>
<td>.032</td>
</tr>
<tr>
<td>HBV DNA &gt;2,000 IU/mL, (%)</td>
<td>91 (20.8)</td>
<td>67 (17.8)</td>
<td>20 (55.6)</td>
<td>.001</td>
</tr>
<tr>
<td>HBV DNA ≤2,000 IU/mL, (%)</td>
<td>46 (10.5)</td>
<td>37 (9.8)</td>
<td>6 (16.7)</td>
<td>.247</td>
</tr>
<tr>
<td>HBV DNA ≤10,000 IU/mL, (%)</td>
<td>19 (4.3)</td>
<td>14 (3.7)</td>
<td>5 (8.3)</td>
<td>.178</td>
</tr>
</tbody>
</table>

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.