DIFFICULT TO TREAT PATIENTS WITH HBeAg NEGATIVE CHRONIC B HEPATITIS

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Abstract. Background. There are 2 billion people infected worldwide, with approximately 5% of the world's population (or 350 million people) being carriers of chronic hepatitis B. [2] Worldwide, chronic hepatitis B is the 10th leading cause of death. HBeAg-negative chronic hepatitis B patients show a lower sustained response to interferon (IFN). Methods. We present two clinical cases of chronic HBeAg negative patients who received several treatments, from standard interferon alpha 2a to nucleoside analogues. Results. In a number of cases, the treatment of chronic HBeAg negative chronic hepatitis B can be a real challenge for the physicians and it is possible that prolonged Peginterferon therapy or addition of nucleot(s) ides analogues may increase the response rate. Keywords: HBeAg negative, Peginterferon alpha 2a, relapse

Introduction

Hepatitis B is found throughout the world but its prevalence varies greatly, being especially high in Asia, sub-Saharan Africa and the South Pacific, as well as in specific populations in South America, the Middle East, and the Arctic[1]. The prevalence in the United States varies based on both the population's characteristics, including the extent of the immigrant population from endemic areas, and on the risk factors and behaviors such as the prevalence of intravenous drug use and homosexual practices. Public health agencies estimate that there are about 1.25 million people infected in the United States, but 2 billion people infected worldwide, with approximately 5% of the world's population (or 350 million people) being carriers of chronic hepatitis B[2]. Worldwide, chronic hepatitis B is the 10th leading cause of death.

Hepatitis B surface antigen (HBsAg) seropositivity for more than six months indicates the presence of hepatitis B viral (HBV) chronic infection. The disappearance of HBsAg from serum with development of the corresponding antibody, anti-HBs, indicates conventional resolution of the infection. HBsAg seroconversion in chronically infected patients is a relatively uncommon event, with an incidence of only 0.8%-2% per year.[3] Chronically infected patients who acquired HBV infection in adulthood[1] have a higher rate of spontaneous HBsAg loss.

Nowadays, there are several antivirals and one
interferon medication used in treating people infected with the hepatitis B virus (HBV). Given the number of treatment options available, it is important to carefully select which drug to use first. For example, use the wrong antiviral and an individual could end up “resistant” to other antiviral drugs.

The choices are complex and highly dependent on the individual’s gender, hepatitis B “e” antigen status (HBeAg), viral load (HBV DNA), HBV genotype or strain and length of infection. The first treatment used should quickly lower the viral load without causing viral resistance and strengthen a person’s immune system so it can control or contain the infection by producing antibodies and attacking HBV-infected liver cells.

People who are HBeAg-negative may also benefit from interferon. Studies show that 63% of the patients treated with pegylated interferon achieved undetectable HBV DNA, and 38% of them achieved normal ALT.

In order to better understand the likelihood of therapeutic response to pegylated interferon in HBeAg negative patients, we present two clinical cases, considered to be “difficult to treat” patients.

Case 1
- Gender: male
- Date of birth: 09.02.1967
- Caucasian
- Date of diagnosis: 2003
- HBsAg positive, HBeAg negative, Anti-HBe positive, Anti Delta negative
- Genotype D
- ALT: 3 x UNL

February 2005:
- Knodell: A8 F1
- ALT > 3 X upper normal limit (UNL)
- HBV-DNA: 1 257 copies/mL
- No antiviral treatment

March 2006:
- ALT: 10 X UNL
- HBV-DNA: 4 862 768 copies/mL
- HBeAg negative, Anti- HBe positive, Anti Delta negative
- Treatment with standard Interferon alpha 2a
  a 3 X 4.5 MIU/week started in June 2006.

December 2006:
- ALT: 10 X UNL
- HBV-DNA: 42 449 774 copies/mL (10 x greater than the viral load at the beginning of therapy)
- Treatment with standard Interferon stopped.

June 2007:
- ALT: 3 x UNL
- HBV-DNA: 156 648 730 copies/mL
- Treatment with Pegasis 180 µg/week started.
- Duration of treatment: 48 weeks (June 2007-May 2008)
- ALT during treatment: normal values

24 weeks after end of treatment (EOT) – December 2008:
- ALT > 2 X UNL
- HBV-DNA: 274 133 468 copies/mL
- Treatment with Lamivudine started in January 2009:
  - 24 weeks (June 2009): ALT = normal values, HBV-DNA: 1 263 copies/mL
  - 48 weeks (December 2009): HBV-DNA: 113 copies/mL

Case 2
- Gender: male
- Date of birth: 15.09.1946
- Caucasian
- Date of diagnosis: 2004
- HBsAg positive, HBeAg negative, Anti-HBe positive, Anti Delta negative
- Genotype D
- ALT: 5 x UNL

April 2005:
- Knodell: A7 F1
- ALT: 5 X UNL
- HBV-DNA: 67 811 536 copies/mL
- Treatment with standard Interferon alpha 2a
  - 3 x 4.5 MIU/week started

August 2006 (24 weeks after EOT):
- ALT: 6 x UNL
- HBV-DNA: 40 691 297 copies/mL
- Lamivudine 100 mg/day started in October 2006

During therapy:
- ALT: normal values, until December 2007 (5 x UNL)
- HBV-DNA at 24 weeks: < 28 copies/mL
HBV-DNA at 48 weeks: 209,784,252 copies/mL
Lamivudine stopped in Dec 2007 (resistance)

January 2008:
- **Pegasys** 180 µg/week started
  - During Pegasys therapy:
    - HBV-DNA at baseline: 209,784,252 copies/mL
    - ALT: 5 X ULN
    - HBV-DNA at week 24: 745,605,918 copies/mL
    - Pegasys stopped in June 2008

September 2008:
- **Entecavir** 1 mg/day started
  - During therapy:
    - ALT: normal values
    - HBV-DNA at week 24: < 51 copies/mL
    - HBV-DNA at week 48: < 51 copies/mL

Conclusions
- Although drug resistance is less of a problem with peginterferon alpha-2a, in some very few cases resistance can occur
- Resistance to Peginterferon was only observed in relapers to standard interferon
- Possibly, prolonged Peginterferon therapy or addition of nucleot(s)ides analogues may increase the response rate

References