Treatment of a Patient with HBeAg-negative Chronic Hepatitis B

ABSTRACT
It is estimated that there are 350 million worldwide carriers of the hepatitis B virus, mostly coming from Asia (Lai et al., 2005). With immigration of Chinese into Western countries, hepatitis B is now becoming established in countries where it was previously uncommon. Chronic hepatitis B infection is a prevalent disease especially in the Toronto and Vancouver areas where most Asians live. Fortunately, over the past decade effective anti-viral treatments have become available. Chronic hepatitis B is mostly an asymptomatic disease, therefore, serological and imaging tests should be used to identify, follow and treat those considered high risk.

KEYWORDS: HBV DNA (hepatitis B DNA), cirrhosis, anti-viral tenofovir, FibroScan

Case Study
Mr. Lee (not his real name) is a 50-year old man who came to Canada in 2003 from China. He is known to be a hepatitis B carrier (HBsAg positive) and was diagnosed over ten years ago. He works as an inspector in the aircraft industry. He lives with his 74 year old natural birth mother who is not a hepatitis B carrier. She was recently vaccinated with free Energix-B from public health. His wife and son are immunized as well.
His blood work shows that he is HBeAg-negative anti-HBeAg positive. HBV DNA measurements have fluctuated from 3,980 IU/mL in March 2009 to 990 IU/mL in October 2011, and are currently 2,420 IU/mL in May 2013. Blood ALT levels are well within the normal range. Platelet counts also reveal low numbers, suggesting possible portal hypertension with hypersplenism.

Mr. Lee was referred to a GI specialist in August 2009. The initial assessment suggested stability due to relatively low HBV DNA and ALT concentrations, but continued monitoring and possible liver biopsy. A biopsy indicated minimally increased chronic inflammation. There was no fibrosis. Abdominal ultrasounds repeated annually beginning in March 2009 showed no abnormalities of the liver.

A FibroScan performed in August 2012 indicated stage 2 fibrosis. However, antiviral therapy was deemed unnecessary at the time due to low HBV DNA values. In October 2012 an abdominal ultrasound revealed moderate attenuation of the ultrasound beam consistent with fatty infiltration.

In May 2013, HBV DNA was The patient had a repeat FibroScan examination which suggested stage 3, or advanced, liver fibrosis. Due to the apparently severe fibrosis, the patient initiated antiviral therapy with tenofovir in June 2013. A third FibroScan was done in July 2013 and suggested stage 1 fibrosis.

Based on these data, the necessity of treatment is unclear. Although HBV DNA and ALT measurements continue to remain low, chronic low platelet counts and slight fibrosis suggest that therapy may be advisable. The patient is approaching his third month of continued treatment. He will be assessed soon to verify the treatment effectiveness.

Discussion

Hepatitis B is a hepadnavirus that infects humans by targeting the liver. It is an infectious disease that is passed through bodily fluids. It is defined as a patient who is HBsAg positive. In the Chinese community, it is mostly vertically transmitted from mother to child upon maternal/fetus blood mixing during delivery. It can be...
passed via sexual contact and use of infected needles from illicit drug use or poorly sterilized medical equipment. Upon infection of a hepatocyte, the viral DNA is used for transcription of viral RNA. Though hepatitis B is not a retrovirus, it uses reverse transcriptase machinery to propagate its infection from synthesized RNA (Liaw and Chu, 2009). Infection over sustained periods of time may result in liver cell damage and hepatic inflammation, which may lead to the development of cirrhosis and/or hepatocellular carcinoma. Male patients infected with hepatitis B have a 25% of developing liver cancer in their lifetime if it is not treated. The risk is even greater after the age of 40 years. Infected female patients can also develop liver cancer, but the risk is lower than for males. Most hepatitis B patients are asymptomatic and only found to be carriers during routine physicals or pregnancy exams. It is the responsibility of the informed physician to be aware of this prevalent disease in Asians which is rare in Westerners.

Chronic hepatitis B infection is generally associated with four phases based on the presence of the hepatitis B e antigen (HBeAg), antibodies to this antigen (anti-HBe), serum alanine aminotransferase (ALT) and hepatitis B DNA (HBV DNA) concentrations in the blood and classified as such.

**Notice the cut off for treatment is lower at DNA >2,000 IU/mL for HBeAg negative disease.**

Chronic hepatitis B infection must be treated with regular follow-ups, blood, and imaging tests (ultrasound and FibroScan) as it is considered to be a chronic disease.

<table>
<thead>
<tr>
<th>Phase</th>
<th>HBe Antigen</th>
<th>Anti-HBe Antigen</th>
<th>HBV DNA (IU/mL)</th>
<th>ALT</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune Tolerant</td>
<td>Positive</td>
<td>Negative</td>
<td>High &gt; 20,000</td>
<td>Normal</td>
<td>Monitor; treat if moderate fibrosis F2 and/or high ALT</td>
</tr>
<tr>
<td>Immune Clearance</td>
<td>Positive</td>
<td>Negative</td>
<td>High &gt; 20,000</td>
<td>High (may fluctuate)</td>
<td>Treat</td>
</tr>
<tr>
<td>Inactive Carrier</td>
<td>Negative</td>
<td>Positive</td>
<td>Low &lt; 2,000</td>
<td>Normal</td>
<td>Monitor</td>
</tr>
<tr>
<td>HBeAg negative Chronic hepatitis</td>
<td>Negative</td>
<td>Positive</td>
<td>High &gt; 2,000</td>
<td>High (may fluctuate)</td>
<td>Monitor; treat if moderate fibrosis or high ALT</td>
</tr>
</tbody>
</table>
An ultrasound every six months to screen for HCC in certain risk groups (e.g., males >40, females >50, cirrhotics regardless of age, family history of HCC) should be considered. Close contacts of the carrier should be vaccinated since the vaccine is very effective and free of charge from public health for household members.

Serologic markers that should be measured on a regular basis are:
- HBV DNA,
- HBeAg,
- anti-HBe,
- ALT,
- AST

Other liver function tests which unfortunately will indicate advanced liver disease when abnormal include:
- INR,
- platelet,
- Imaging tests
- ultrasound (looking for hepatomas)
- FibroScan (looking for degree of fibrosis)

In HBeAg-positive disease, treatment should be considered when HBV DNA > 20,000 IU/mL and ALT is 2X upper limit of normal. In HBeAg negative stage, treatment should be considered when HBV DNA is > 2,000 IU/mL and ALT 2X ULN.

However, treatment can also be considered if the person is older than 35 years of age, which a DNA > 20,000 for HBeAg+ carriers or DNA >2000 for HBeAg negative carriers, and a FibroScan or FibroTest shows at least moderate fibrosis (F2).

In patients in a “grey zone” of treatment, one can argue that Fibroscans can play a role in the decision for treatment. Fibroscan®, also called transient elastography, is a recent non-invasive, painless technique that uses ultrasound to assess liver stiffness (measured in kPa correlated to fibrosis). The greater the liver stiffness means the greater likelihood of liver fibrosis (scarring) or cirrhosis. The scores range from F0 - zero fibrosis to F4 - cirrhosis. It is a predictor of mortality and has similar accuracy to liver biopsy. However, since the FibroScan is non-invasive, it can be repeated regularly to monitor changes in fibrosis over time (e.g., due to disease progression and regression of fibrosis with effective therapy). There may be variability in liver stiffness measurements using the FibroScan.
Figure 1: Common Chronic Liver Diseases

- **Healthy liver**
- **Alcoholic liver disease**
  - Fatty change, or steatosis
  - Acute hepatitis or inflammatory reaction to the cells affected by fatty change
  - May progress to cirrhosis
- **Viral Hepatitis B**
  - Acute hepatitis causes inflammatory reaction to cell injury and necrosis
  - Chronic hepatitis has sustained inflammation
  - Includes cell necrosis, inflammation, fibrosis, and cirrhosis
- **Primary Biliary Cirrhosis**
  - Inflammation and scarring destroy the small ducts within the liver, slowing or blocking normal flow of bile
  - Inflammation spreads to nearby liver cells which are destroyed and then replaced by scar tissue (fibrosis)
- **Nonalcoholic fatty liver disease**
  - Liver enlarges with fat deposits
  - Scar tissue forms
  - Can be severe and lead to cirrhosis
- **Autoimmune Hepatitis**
  - Portal and periportal chronic inflammation
  - Bile duct lesions may be present
  - Connective tissue replaces the lost parenchyma
  - Portal tract is expanded and assumes a "maple leaf" configuration
  - Cirrhosis may follow
Treatment of a HBeAg negative Hepatitis B patient

### SUMMARY OF KEY POINTS

<table>
<thead>
<tr>
<th>Hepatitis B is a hepadnavirus that infects humans by targeting the liver.</th>
<th>Infection over sustained periods of time may result in liver cell damage developing liver cirrhosis and cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B is an infectious disease that is passed through bodily fluids.</td>
<td>Most hepatitis B patients are asymptomatic and only found to be carriers during routine physicals or pregnancy exams.</td>
</tr>
</tbody>
</table>

(e.g., due to obesity); therefore, expert interpretation is necessary. Availability of FibroScans in Canada is increasing, but the provincial health plans (except in Quebec) do not yet reimburse the test. The cost is approximately $100 in private clinics (www.liverscan.ca).

High HBV DNA levels and normal ALT should be treated if the FibroScan suggests moderate fibrosis (F2).

Pregnant patients with a high HBV DNA may be treated in the third trimester to prevent transmission to the baby. There is still a 4% chance of transmission to the child even with immediate postpartum vaccination.

There several treatments available for hepatitis B, ranging from interferon injections (interferon alpha, pegylated interferon) which are poorly tolerated to orally taken nucleotide analogs (NAs). The older anti-virals (e.g., lamivudine) have a likelihood of developing drug resistance. The newer agents (e.g., tenofovir and entecavir) are well tolerated. Both agents will drop the HBV DNA level drastically within a couple months of use; tenofovir has not yet been associated with antiviral resistance. There is new evidence that

### CLINICAL PEARLS

HEPATITIS B infection is a chronic disease (which like diabetes or hypertension) needs to be followed-up and monitored (blood tests, ultrasound, FibroScan) on a regular basis. Immunize contacts.

Treat at risk patients for obviously HIGH HBV DNA and ALT. FibroScan at risk patients. Refer when unsure.
treatment with potent NAs such as tenofovir and entecavir lead to fibrosis regression, even reversal of cirrhosis, as well as reduction in the incidence of liver cancer. However, the relative expense of these medications may represent a barrier to those who cannot afford it.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon Alpha</td>
<td>(Intron A) is given by injection several times a week for six months to a year, or sometimes longer. The drug can cause side effects such as flu-like symptoms, depression, and headaches. Approved 1991 and available for both children and adults.</td>
</tr>
<tr>
<td>Pegylated Interferon</td>
<td>(Pegasys) is given by injection once a week usually for six months to a year. The drug can cause side effects such as flu-like symptoms and depression. Approved May 2005 and available only for adults.</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>(Epivir-HBV, Zeffix, or Heptodin) is a pill that is taken once a day, with few side effects, for at least one year or longer. Approved 1998 and available for both children and adults.</td>
</tr>
<tr>
<td>Adefovir Dipivoxil</td>
<td>(Hepsera) is a pill taken once a day, with few side effects, for at least one year or longer. Approved September 2002 for adults. Pediatric clinical trials are in progress.</td>
</tr>
<tr>
<td>Entecavir</td>
<td>(Baraclude) is a pill taken once a day, with few side effects, for at least one year or longer. Approved April 2005 for adults. Pediatric clinical trials are in progress.</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>(Tyzeka, Sebivo) is a pill taken once a day, with few side effects, for at least one year or longer. Approved October 2006 for adults.</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>(Viread) is a pill taken once a day, with few side effects, for at least one year or longer. Approved August 2008 for adults.</td>
</tr>
</tbody>
</table>