Intervention in chronic hepatitis B infection: Why, when and how?

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Case commentary: Management choices for an HBeAg-positive patient

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Case commentary: Long-term antiviral therapy for HBeAg-negative disease

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Chronic hepatitis B infection
Clinical concepts and effective interventions

Faculty and content outline

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Learning objectives

Upon completion of this activity, readers should be able to:

• **Describe** the epidemiology and natural history of chronic hepatitis B (CHB) infection in Europe

• **Evaluate** the efficacy of available agents in the management of HBeAg-positive and HBeAg-negative CHB infection

• **Assess** the impact of resistance on clinical outcome and discuss strategies to manage treatment-emergent resistance.

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Epidemiology of hepatitis B virus infection and the burden of chronic disease

Chronic hepatitis B virus (HBV) infection is estimated to affect more than 350 million individuals worldwide. Chronic hepatitis B (CHB) is placed among the top ten infectious causes of death globally. In Europe, an area of overall low-to-intermediate prevalence, it is estimated that there are up to 3.5 million chronic HBV carriers. The prevalence varies between countries and between population subgroups in each country. Eastern Europe, Russia and the Mediterranean countries have an intermediate prevalence of chronic infection (1–8%), while Northwestern Europe has low HBV endemicity (<1%).

In Northwestern Europe, the majority of individuals contract their infection in early adulthood through sexual transmission or injection drug use with contaminated needles. In areas of intermediate endemicity, transmission during the perinatal period or from infected household contacts is also important. According to the World Health Organisation (WHO), the incidence of HBV infection varies from 0–10 per 100,000 persons in the majority of Western Europe, to 10–50 per 100,000 persons in Eastern European countries. However, population migration from areas of high endemicity is changing the profile of HBV infection across Europe, with pockets of higher prevalence of chronic infection in countries with overall low HBV endemicity. For example, a recent survey indicated that the prevalence of hepatitis B surface antigen (HBsAg) positivity in France rose from 0.2–0.4% in the early 1990s to 0.65% in 2003–2004. The highest rates of carriage were observed in individuals born in sub-Saharan Africa or in the Middle East (5.25% and 2.45%, respectively).

Table 1 shows the groups of individuals that should be screened for the presence of HBsAg and hepatitis B core antibodies (anti-HBc). HBsAg-positive individuals should be assessed for evidence of active replication and liver disease.

Natural history of disease and factors influencing disease course

CHB can result in serious sequelae, including cirrhosis, end-stage liver disease and hepatocellular carcinoma. The cumulative five-year rate of progression to cirrhosis in HBeAg-positive patients ranges from 8% to 20%. The risk of hepatocellular carcinoma is high in patients with cirrhosis (4–6% per year). The cost of care rises sharply with disease progression and varies between countries. A recent study reported that the average annual cost of care in France in 2001 rose from €1093 for CHB to €8842 for patients with decompensated cirrhosis.

Chronic HBV infection evolves through several successive disease stages (Figure 1). However, individuals do not always progress through the stages in a linear manner.

The immunotolerant phase, which immediately follows the acute episode, is characterised by active viral replication and a weak host immune response leading to high serum levels of HBV DNA, generally associated with the presence of hepatitis B e antigen (HBeAg), minimal histologic activity and an absence of symptoms. This stage may persist for many years, particularly in those infected perinatally or during early childhood.
Clinical concepts and effective interventions

Chronic hepatitis B infection

During the immuno-elimination phase, active inflammatory liver disease occurs as a result of the host’s immune response to the presence of HBV. HBV DNA levels fall to lower levels and are sometimes fluctuating, while alanine aminotransferase (ALT) levels are elevated, signalling destruction of hepatocytes by the immune system. The cycle of hepatic damage and repair results in symptomatic disease and progressive liver damage, i.e. CHB. Some patients with CHB have detectable HBeAg. These patients may experience spontaneous loss of HBeAg and seroconversion to anti-HBe at a rate of approximately 1–10% per year,10,11 and enter the asymptomatic carrier state.

However, the vast majority of patients with CHB in Europe are HBeAg-negative, anti-HBe-positive. The proportion of patients with HBeAg-negative disease is rising in Europe. HBeAg-negative disease occurs as a result of mutations in the precore region (stop codon at position 1896) and the basal core promoter region (nucleotide substitutions at positions 1762 and 1764) which halt or down-regulate production of HBeAg.12 During or after HBeAg loss or seroconversion to anti-HBe antibodies, immune pressure on the wild-type virus probably leads to selection of the HBeAg-negative variants as the dominant viral variants.

Following HBeAg seroconversion, individuals may enter a non-replicative stage, the “inactive” HBV carrier stage. Inactive disease is characterised by the presence of HBsAg in the serum, low or undetectable levels of HBV DNA, normal ALT activity and the absence of HBeAg.4 However, these patients are at risk for disease reactivation, for example if they are treated with immunosuppressive medications, and should undergo regular monitoring. Inactive carriers with cirrhosis should also be closely monitored as they are at risk of developing hepatocellular carcinoma, regardless of the level of HBV replication. A minority of inactive HBV carriers undergo spontaneous HBsAg seroconversion. However, this occurs in less than 1% per year.20

Who should be treated?

As suggested in the recently published American Association for the Study of Liver Diseases (AASLD) Practice Guideline, careful consideration of the patient’s age, severity of liver disease, likelihood of response, and potential adverse events is needed before treatment is initiated.21 Continued monitoring of HBV-infected patients is essential for risk assessment. Treatment is indicated if the risk of liver-related morbidity and mortality in the near and foreseeable future (5–20 years) and the likelihood of achieving maintained viral suppression after a defined course of treatment or during continued treatment are high. Conversely, treatment is not indicated if the risk of liver-related morbidity or mortality in the next 20 years and the likelihood of achieving sustained viral suppression are low.21

Patients with HBeAg-positive CHB should be treated when ALT levels are greater than twice the upper limit of normal (2 x ULN) or the patient has moderate-to-severe hepatitis on liver biopsy, and a serum HBV DNA level greater than 20,000 international units (IU) per millilitre. Treatment should be delayed for 3–6 months in individuals with compensated liver disease to determine if spontaneous HBeAg seroconversion occurs, whereas patients with icteric ALT flares should be treated promptly.4,21

Patients with HBeAg-negative CHB, a serum HBV DNA level greater than 20,000 IU/mL and elevated ALT >2 x ULN should be considered for treatment. Liver biopsy may be considered for lower HBV DNA levels (2000–20,000 IU/mL) and borderline, normal or minimally elevated ALT levels. In this group of patients treatment may be initiated if there is moderate/severe inflammation or significant fibrosis on liver biopsy.4,21

Patients who have failed to respond to prior interferon (IFN) alfa or nucleoside/nucleotide analogue therapy should be retreated. All patients with virologic breakthrough should be considered for rescue therapy with an alternative treatment schedule.21

Treatment should also be considered in patients with compensated cirrhosis with a serum ALT level >2 x ULN, and those with normal or minimally elevated ALT levels if serum HBV DNA levels are high (>2000 IU/mL). In patients with decompensated cirrhosis, treatment should be initiated promptly.21

Treatment options

Five agents are currently licensed in Europe for the treatment of chronic HBV infection. They can be divided into alfa IFNs (standard IFN alfa, pegylated IFN alfa) and nucleoside/nucleotide analogues (lamivudine, adefovir, entecavir). There are also a number of agents in development, including telbivudine which is currently being assessed by the European Agency for the Evaluation of Medicinal Products (EMEA) and should be approved very soon. Tenofovir, and the other antiviral agents, are all nucleoside analogues that inhibit HBV reverse transcriptase. They are not substrates for the HBV DNA polymerase and therefore can be used for long-term treatment with only minimal development of resistance. Entecavir is currently the only licensed agent with activity against both HBeAg-positive and HBeAg-negative disease. In contrast, adefovir is only active against HBeAg-positive CHB.

Interferon alfa

Interferon alfa-2a or -2b was the first agent available for the treatment of chronic HBV infection. Standard IFN alfa treatment requires subcutaneous injections. It is administered for 16–24 weeks for HBeAg-positive CHB and 48 weeks for HBeAg-negative disease. A meta-analysis of IFN studies in HBeAg-positive CHB (total n=837 patients) reported that 37% of patients experienced HBV DNA suppression to less than 10^5 copies/mL, 33% had loss of HBeAg and 8% had sustained viral suppression are low.21

Pegylated IFN alfa-2a offers the advantage of once-weekly subcutaneous administration at a dose of 180 µg for 48 weeks, in both HBeAg-positive and HBeAg-negative patients. It was evaluated with substantially more sensitive HBV DNA assays than used in pivotal trials of conventional IFNs. In
Table 2 summarises the results of IFN trials in the treatment of chronic HBV infection.

**Nucleoside/nucleotide analogues**

Nucleoside/nucleotide analogues are administered orally. The agents are administered once a day and dose varies with each agent: lamivudine 100 mg; adefovir 10 mg; entecavir 0.5 mg in nucleoside-naïve patients, 1.0 mg in lamivudine-refractory patients; telbivudine 600 mg. All of the nucleoside/nucleotide analogues result in viral suppression, normalisation of ALT, improved histology and positive clinical outcomes in a substantial proportion of patients.

The clinical use of nucleoside/nucleotide analogues depends on their respective intrinsic antiviral potencies and resistance profiles (including cross-resistance). Mean log10 reduction in viral load after one year of therapy in HBeAg-positive patients is greatest on average with entecavir (−6.9 log10 copies/mL), compared with telbivudine (−6.5 log10 copies/mL), lamivudine (−4.0 to −5.5 log10 copies/mL), and adefovir (−3.5 log10 copies/mL). In HBeAg-negative disease, 48 weeks of therapy results in suppression of HBV DNA to less than 400 copies/mL in 51%, 61% and 91% of patients receiving adefovir, lamivudine and entecavir, respectively. (These figures are taken from non-comparative studies.) 30–32 Long-term data are now becoming available that demonstrate increasing response rates with long-term therapy. Tenofovir is more potent than telbivudine (−6.5 log10 copies/mL), lamivudine (−4.0 to −5.5 log10 copies/mL), and adefovir (−3.5 log10 copies/mL).32–34 In HBeAg-negative patients, 48 weeks of therapy resulted in suppression of HBV DNA to <400 copies/mL in 25% of patients, normalisation of ALT in 46% and HBeAg seroconversion in 24% of the cohort studied.35 However, 24 weeks after cessation of treatment, only 14% had HBV DNA levels <400 copies/mL. With increasing length of follow-up, HBeAg seroconversion rates rose, being 42% 48 weeks after cessation of treatment.36 In HBeAg-negative patients, 48 weeks of pegylated IFN alfa-2a resulted in HBV DNA levels <400 copies/mL in 73% of cases and five patients underwent seroconversion to anti-HBs antibodies.37 However, 12 months after treatment cessation, only 17% of patients had undetectable HBV DNA.38

Table 2 summarises the results of IFN trials in the treatment of chronic HBV infection.

<table>
<thead>
<tr>
<th>Nucleoside/nucleotide analogue</th>
<th>Lamivudine 100 mg qd 48–52 weeks</th>
<th>Adefovir 10 mg qd 48 weeks</th>
<th>Entecavir 0.5 mg qd 48 weeks</th>
<th>Telbivudine 600 mg qd 52 weeks</th>
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<tr>
<td>HBeAg-positive chronic hepatitis B</td>
<td>Loss of serum HBV DNA* (%)</td>
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<td>21</td>
<td>67</td>
</tr>
<tr>
<td>Loss of HBeAg (%)</td>
<td>17–32</td>
<td>24</td>
<td>22</td>
<td>26</td>
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<tr>
<td>HBeAg seroconversion (%)</td>
<td>16–21</td>
<td>12</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>Loss of HBsAg (%)</td>
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<td>0</td>
<td>2</td>
<td>0</td>
</tr>
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<td>ALT normalisation (%)</td>
<td>41–75</td>
<td>48</td>
<td>68</td>
<td>77</td>
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<tr>
<td>Histologic improvement (%)</td>
<td>49–56</td>
<td>53</td>
<td>72</td>
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<td>Durability of response (%)</td>
<td>50–80*</td>
<td>−90</td>
<td>69*</td>
<td>80</td>
</tr>
<tr>
<td>HBeAg-negative chronic hepatitis B</td>
<td>Loss of serum HBV DNA* (%)</td>
<td>60–73</td>
<td>51</td>
<td>90</td>
</tr>
<tr>
<td>Loss of HBeAg (%)</td>
<td>60–79</td>
<td>72</td>
<td>78</td>
<td>74</td>
</tr>
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<td>Histologic improvement (%)</td>
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<td>NA</td>
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<tr>
<td>Durability of response (%)</td>
<td>50–80*</td>
<td>−90</td>
<td>69*</td>
<td>80</td>
</tr>
</tbody>
</table>

*Lower limit of detection of the assay: 20,000–200,000 IU/mL for standard IFN trials, approximately 50 IU/mL for pegylated IFN trials; †Response at weeks 48 and 72; ‡Liver biopsy at week 72; ††No or short duration of consolidation treatment.

Table 3. Results of nucleoside/nucleotide analogue trials in patients with HBeAg-positive and HBeAg-negative CHB (adapted from ref. 21). NA: not available

Resistance to telbivudine occurs in 22% and 9% of treatment-naïve HBeAg-positive and -negative patients, respectively, after one year of administration, with all resistant variants bearing the M204I (YIDD) substitution.39 Full resistance to entecavir is the result of a three-step selection-mutation accumulation process, involving a sequence of lamivudine resistance substitutions at position 204 (M204V and M204I), the rtL180M substitution that improves the
Replication capacity of lamivudine-resistant variants and one or more of the entecavir-specific substitutions (T184A/I/L, S202G/C and M250V) that restore full replication in the presence of entecavir. The cumulative probability of virological breakthrough due to entecavir resistance is 0.8% in treatment-naive patients, but in the order of 39.5% in lamivudine-refractory patients after four years of administration.

HBV resistance to adefovir dipivoxil is complex. Long-term administration has been shown to select variants bearing N236T or A181V. The emergence of adefovir resistance is slow, but after five years of monotherapy, adefovir-resistant variants have been selected in 29% of cases. Mutations that confer resistance to adefovir do not confer significant cross-resistance to lamivudine, telbivudine or entecavir, except maybe the A181T substitution which could confer reduced susceptibility to lamivudine. Tenofovir is approved for use in the treatment of HIV infection only, but Phase III clinical trials are ongoing in HBV infection. No resistance mutation has been clearly identified so far for tenofovir, which exhibits no cross-resistance in vitro with lamivudine, telbivudine or entecavir.

**Treatment endpoints**

Determining the endpoints for therapy is crucial in the management of chronic HBV infection as eradication is not achievable with the currently available agents. Virologic, biochemical, serologic and clinical endpoints can be utilised (Figure 2). Seroconversion to anti-HBs is the ideal endpoint, however this is rarely achieved. In patients with HBeAg-positive CHB, seroconversion to anti-HBs antibodies with low or undetectable levels of HBV DNA and normalisation of ALT is the goal. This goal can be achieved with short-term therapy in some HBeAg-positive patients. In patients with HBeAg-negative disease, and in those with HBeAg-positive CHB who failed to achieve HBeAg seroconversion after short-term therapy, the goal is sustained viral suppression that will ensure decreased hepatic necroinflammation and prevention of the onset of liver disease complications.

**How to treat?**

There is currently no clear consensus on the indications for HBV therapy. Schematically, short-term pegylated IFN alfa therapy is indicated for HBeAg-positive patients with a high likelihood of HBeAg seroconversion (such as patients with low viral load and high serum aminotransferase levels). However, it has recently been suggested that similar HBeAg seroconversion rates can be achieved with two to three years of oral nucleoside/nucleotide analogue therapy (probably in the same subgroups of patients) with a better side-effect profile.

In HBeAg-negative patients, HBeAg-positive patients with a low likelihood of HBeAg seroconversion, and those who failed to seroconvert during IFN alfa therapy, nucleoside/nucleotide inhibitors should be used. In most cases, they will need to be administered for life, because these drugs are only virustatic and viral replication restarts soon after their withdrawal and liver disease again begins to progress.

- In treatment-naïve patients: Given the fact that analogues will have to be given for many years and the likelihood of early resistance emergence with lamivudine, adefovir or telbivudine, these drugs should probably be used in combination in order to avoid cross-resistance, i.e., lamivudine plus adefovir or telbivudine plus adefovir. However, given its favourable resistance profile and pending new data with longer follow-up entecavir can be used as monotherapy in patients with no to moderate fibrosis. In patients with the most severe infection, one should be cautious and use a combination of lamivudine, telbivudine or entecavir with adefovir. In sub-optimal responders to adefovir, tenofovir can be used. Tenofovir will probably replace adefovir in these combinations if it is approved.

- In lamivudine-refractory patients, studies have reported the efficacy of combination therapy with lamivudine and adefovir/tenofovir, or switching to entecavir. Future studies may confirm other strategies, e.g., entecavir plus adefovir or, when approved, tenofovir.

**How to monitor therapy?**

For IFN-based therapy, treatment failure is defined as failure to achieve HBeAg seroconversion during or after therapy. Such a failure can be anticipated if the HBV DNA reduction at six months of therapy is moderate or nil. Non-response to nucleoside/nucleotide analogue therapy, also called primary treatment failure, is the failure to achieve a more than 1 log10 HBV DNA decrease during the first three months of therapy. Some patients may experience a sub-optimal response, characterised by a decrease of more than 1 log10 but less than 2–3 log10 at month 3 of therapy. Secondary antiviral treatment failure is defined by a rebound of serum HBV DNA of more than 1 log10 above the nadir in patients who initially responded. The emergence of antiviral drug resistance is the principal cause of secondary treatment failure.

In clinical practice, assessments of HBV DNA, ALT and HBeAg/anti-HBe should be performed at baseline and then every three months. If a patient is suspected of having primary or secondary treatment failure without ALT elevation, this should be confirmed by a second HBV DNA level measurement. In the case of primary or secondary treatment failure, a patient’s compliance should be assessed, if necessary by means of drug dosages. In compliant patients, resistance testing is more and more widely used to demonstrate resistance and enable an informed treatment decision. However, consensus guidelines will need to be issued in the near future to guide treatment decisions according to the patient’s resistance profile.
Impact of successful therapy

The currently available treatment options cannot eradicate HBV because of the persistence of covalently closed circular proviral DNA (cccDNA) in the nuclei of hepatocytes. However, a number of studies have demonstrated the beneficial impact of treatment intervention on clinical outcome. Niederau and colleagues have demonstrated that HBeAg loss during conventional IFN alfa therapy was associated with significantly longer overall survival and survival without complications. The study by Liaw and colleagues investigating the impact of lamivudine therapy in patients with cirrhosis or advanced fibrosis reported that lamivudine was associated with a lower incidence of disease progression than placebo. However, the selection of lamivudine-resistant mutations attenuated the positive benefit of lamivudine therapy.

More recently, a five-year study of adefovir in HBeAg-negative patients has reported improvements in hepatic fibrosis: 71% of patients demonstrated a more than one-point decrease in Ishak fibrosis score after five years of continuous therapy. Improvements in histologic assessments have also been reported with entecavir. In nucleoside-naïve patients, 48 weeks of entecavir therapy is associated with histologic improvement (defined as a more than two-point improvement in Knodell necroinflammatory score and no worsening of Knodell fibrosis score) in 72% and 70% of HBeAg-positive and HBeAg-negative patients, respectively. Meanwhile, 48 weeks of treatment with pegylated IFN alfa-2a results in histologic improvement in 38% and 15% of HBeAg-positive and HBeAg-negative patients, respectively.

Conclusions

Chronic HBV infection is a serious public health concern, with approximately 3.5 million individuals in Europe chronically infected. The profile of the disease is changing with the number of HBeAg-negative cases rising and population migration having a significant impact. Effective identification of chronically infected individuals and optimal intervention is vital to reduce the risk of disease progression. The evolving data surrounding the natural history of CHB and the impact of treatment, coupled with the availability of better agents, will result in a shift in treatment paradigms.

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Case commentary: Management choices for an HBeAg-positive patient

Michael Manns, MD, Katja Deterding, MD

Introduction

This case commentary concerns a patient who was HBeAg-positive at admission and who developed complications including drug resistance. This case highlights the pros and cons of different strategies for treating chronic hepatitis B.

Case report and discussion

A 27-year-old woman with chronic hepatitis B infection was admitted to the out-patient clinic for the first time in June 2002. She was known to have been infected with hepatitis B virus (HBV) since 1995, however, the mode of transmission was unknown.

Her transaminase levels were highly elevated: her alanine aminotransferase (ALT) was 244 U/L (normal range <17 U/L), and her aspartate aminotransferase (AST) was 200 U/L (normal range <15 U/L).

She was HBsAg-positive and HBeAg-positive with high viraemia. As the patient was a medical student, it was decided to start antiviral treatment with peginterferon alfa-2a 180 µg once a week in August 2002. At that time no liver biopsy was available.

Is a liver biopsy necessary to start antiviral treatment in HBeAg-positive hepatitis B?

Liver biopsy is most helpful in individuals who do not clearly meet current guidelines for treatment. As recommended in international guidelines, liver biopsy should be considered for patients who are HBsAg-positive with HBV DNA levels higher than 20,000 IU/mL (10^5 copies/mL) with either elevated ALT levels of 1–2 x ULN (for a 3–6 month period), or who remain HBeAg-positive with HBV DNA levels >20,000 IU/mL (10^5 copies/mL) and are >40 years old. Treatment should be considered if the biopsy shows moderate/severe inflammation or significant fibrosis. However, in our case treatment was indicated irrespective of liver biopsy because the patient was a medical student and high HBV DNA levels indicate infectivity which may result in loss of employment for medical health professionals.

Nevertheless, liver biopsy is still very useful and should be recommended to exclude other causes of liver disease. Moreover, even patients with normal transaminase levels can develop cirrhosis, thus we believe that a biopsy might be even more relevant in patients with normal or minimally elevated transaminases.

Was interferon-based therapy indicated in this patient?

The following factors are known to be positively associated with interferon response:

- transaminase levels at least twice the upper limit of normal (2 x ULN)
- low viral load, <200,000 IU/mL (<10^6 copies/mL)
- HBV genotype A
- no previous antiviral therapy

Our patient fulfilled two of these criteria: she had received no antiviral treatment in the past and her transaminase levels were >2 x ULN.

Interferon alfa has been shown to be effective in suppression of HBV replication and in inducing remission of liver disease. HBsAg clearance is possible in up to 20% after five years of follow-up. Recent studies have shown that patients infected with HBV genotypes A and B respond better to interferon alfa than those infected with genotypes C and D. Peginterferon alfa has the advantages of more convenient administration and more sustained viral suppression. It has also been shown that a higher proportion of patients who received peginterferon alfa will seroconvert to anti-HBe than those treated with standard interferon alfa. The recommended duration of treatment with peginterferon alfa for HBeAg-positive chronic hepatitis B patients in the EU is currently 48 weeks; although ongoing studies are evaluating a shorter duration of treatment (24 weeks). Interferon can be associated with significant side effects, including flu-like symptoms, weight loss, thrombocytopenia, hypo- or hyperthyroidism, anxiety, depression, and suicidal tendency.

Case continues

The patient developed breakthrough during interferon therapy and, in January 2003, the therapy was stopped. In April 2003, HBV replication was still detectable and therefore antiviral therapy with lamivudine 100 mg daily was started.

The patient became pregnant six months after the start of lamivudine therapy. She decided to continue her pregnancy and to continue lamivudine therapy. The pregnancy continued without any complications and a healthy child was born in Spring 2004.
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Lamivudine therapy was administered continuously until 2004. In June 2004, her HBV DNA level increased to over $18 \times 10^6$ IU/mL, although her transaminase levels were still normal. This corresponded to an increase in serum HBV DNA levels by more than 1 log$_{10}$ IU/mL during therapy, compared to the nadir. Serum was tested for antiviral-resistant HBV mutants and the L180M mutation, associated with lamivudine resistance, was detected. Accordingly, therapy was switched to adefovir 10 mg per day and her HBV DNA decreased over the next few months. The patient took adefovir 10 mg daily until November 2006 when her HBV DNA levels increased again to over $3.88 \times 10^6$ IU/mL. Analysis at this time demonstrated the N236T mutation, which is associated with adefovir resistance.

Since the patient wanted to become pregnant again, therapy was stopped. She had no clinical or biochemical signs of impaired liver function, and it was intended that a liver biopsy would be performed after delivery and therapy would be reinstated if histological signs of fibrosis are present.

How to select the optimal nucleoside or nucleotide therapy to treat HBeAg-positive hepatitis B

Currently lamivudine, adefovir, entecavir and telbivudine (in the USA and Switzerland) are licensed for antiviral treatment in chronic hepatitis B patients.

An antiviral agent should be chosen based on the following criteria:

- **efficacy**
- **durability of response**
- **resistance profile**
- **status of the liver disease**

Table 1 shows the efficacy of the nucleos(t)ide analogues currently licensed for antiviral treatment in chronic hepatitis B patients, and the respective incidence of genotypic resistance.

![Table 1. Efficacy of and incidence of genotypic resistance to currently licensed antiviral agents](image)

In choosing which antiviral agent to use, consideration should be given to safety, efficacy and risk of treatment-emergent resistance. For HBeAg-positive chronic hepatitis B it is recommended that treatment should be continued until the patient has achieved HBeAg seroconversion and completed at least six months of additional therapy after appearance of anti-HBe antibodies.

In patients receiving antiviral therapy, HBV DNA should be measured every 3–6 months.

How to manage lamivudine resistance in HBeAg-positive hepatitis B

Lamivudine should not be continued as monotherapy when resistance has developed since continued lamivudine in the presence of resistance has no clinical benefit. Moreover, compensatory mutations can occur which may limit the subsequent use of other antivirals. Fortunately, adefovir and entecavir (but not telbivudine) are effective against lamivudine-resistant hepatitis B. Recent studies have shown that adefovir should be used as an “add on strategy” with lamivudine. In one study, adefovir resistance was less frequently detected in patients who received adefovir in addition to lamivudine than in patients who switched to adefovir monotherapy. Up to 20–30% of patients treated with adefovir monotherapy may show a sub-optimal response. In these cases switching from adefovir monotherapy to tenofovir monotherapy could be an effective strategy since, in a recent pilot trial, almost all patients who were switched from adefovir to tenofovir showed a rapid response (within six months).

Entecavir is also effective in patients with lamivudine resistance and high viraemia (>200,000 IU/mL; >$10^8$ copies/mL). It has been shown that entecavir therapy is associated with biochemical response, however there is an increased risk of resistance to entecavir treatment in these patients; overall virologic rebounds due to entecavir resistance were observed in 15–19% after 144 weeks of therapy.

How to manage adefovir resistance in HBeAg-positive hepatitis B

When secondary resistance to adefovir arises in patients without prior lamivudine treatment, therapy can be switched to entecavir, telbivudine or lamivudine.
In cases of secondary treatment failure with adefovir in lamivudine pre-treated patients, lamivudine can be replaced by entecavir. Tenofovir is not recommended because of cross-resistance with adefovir.14 The likelihood of resistance in individual patients is often related to their age, the severity of the underlying liver disease and the intensity of their hepatitis flare.

How can we prevent resistance?

Antiviral treatment should only be used as needed. The indication for antiviral treatment should be reviewed and the benefit–risk ratio assessed.

Tolerable and convenient regimens should be used to encourage patient compliance. Importantly, drugs with optimal antiviral potency should be given. In the case presented here, adefovir and entecavir were not available when treatment was commenced. Today, lamivudine monotherapy is not recommended because of the very high incidence of resistance with monotherapy.

During the clinical course, an alternative antiviral agent should be given if HBV DNA is >6 log_{10} after the initial 12 months of monotherapy, and cross-resistant drugs should be avoided.

To maximise genetic barriers to resistance, drugs with low incidence of resistance over time should be used, while sequential monotherapy and treatment interruptions should be avoided. The implications of treatment-emergent resistance on the availability of future effective options should be considered. Although data are limited, first-line combination therapy may be considered.

How to manage pregnancy during antiviral therapy of HBeAg-positive hepatitis B

A general recommendation for antiviral therapy during pregnancy cannot be given because there are insufficient data. Peginterferon alfa is contraindicated. Nucleos(t)ide analogues should only be used in the last trimester after balancing the risks for mother and child. However, based on experience with HBV- and HIV-infected patients, lamivudine seems to be relatively safe, while to date only limited data are available for adefovir and entecavir.

Conclusion

In conclusion, our case highlights problems in the long-term management of HBeAg-positive hepatitis B. The emergence of resistance can limit the effectiveness of antiviral therapy and potentially worsen liver disease. Consideration of efficacy and resistance patterns is important when planning and administering effective antiviral therapy. In addition, monitoring for drug resistance every three to six months during antiviral therapy is crucial for hepatitis B patients.

References

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Case commentary: Long-term antiviral therapy for HBeAg-negative disease
Cihan Yurdaydin, MD

Case history

In July 2001, a 55-year-old woman visited the outpatient clinic of the University of Ankara Medical School for work-up of known chronic hepatitis B of three years’ duration. She had been diagnosed with hepatitis B after she learned that her sister was diagnosed with chronic hepatitis B. On work-up of her newly diagnosed hepatitis B by a gastroenterologist, her HBV DNA was “undetectable” by hybridisation assay on two occasions, although her alanine aminotransferase (ALT) levels were found to be slightly elevated, between 1.5 and 2 times the upper limit of normal (ULN). The patient was HBeAg-negative and anti-HBe-positive. An ultrasound examination demonstrated increased echogenicity of the liver architecture. Her physician suggested that the slight elevations of liver enzymes were most likely due to non-alcoholic steatohepatitis and advocated exercise and weight loss. She initially lost some weight but regained it and was unsure about the effect of weight loss on her liver biochemistry.

When first seen at the University of Ankara Medical School, she was asymptomatic and her physical examination was normal. Her height was 1.64 m and she weighed 71 kg (body mass index (BMI) 26.4). The laboratory examination showed an ALT of 61 U/L (normal value ≤37 U/L) and an AST (aspartate aminotransferase) of 46 U/L. Total bilirubin, alkaline phosphatase, gamma-glutamyl transpeptidase, prothrombin time, and complete blood count were all within normal limits. HBV DNA was undetectable by a hybridisation assay but was 3 × 10^5 copies/mL by a PCR-based assay. Serology testing revealed that she was HBeAg-negative and anti-HBe-positive. A liver biopsy showed chronic active hepatitis with bridging fibrosis (Stage 3 fibrosis and a histologic activity index of 12 according to Knodell). The patient was prescribed lamivudine 100 mg daily, which at the time was the only licensed nucleos(t)ide analogue.

Case commentary

HBeAg-negative disease is a late stage in the natural history of chronic hepatitis B (CHB) infection. It occurs when HBV variants with mutations in the precore and/or core region of the HBV genome prevail. This phase of the disease poses a serious challenge for patients and clinicians alike, not only because it may be more difficult to treat than HBeAg-positive CHB, but also because of the potential misdiagnosis of patients as inactive HBsAg carriers.

The inactive HBsAg carrier is characterised by a known history of HBsAg-positivity in serum of at least six months, persistently normal serum aminotransferases, undetectable HBV DNA by non-proliferative assays or HBV DNA below 10^5 or 10^4 copies/mL by PCR-based assays, and minimal or no necroinflammatory activity on liver biopsy. However, liver biopsy is not an absolute requirement for the diagnosis of the inactive HBsAg carrier state.

In this case, it appears that, for three years after diagnosis, the patient was considered by her gastroenterologist to be an inactive HBsAg carrier based on two HBV DNA determinations. What was the reason for the misdiagnosis? First of all, HBeAg-negative CHB patients generally have lower serum HBV DNA levels than HBeAg-positive CHB patients. The cut-off level of approximately 10^5–10^6 copies/mL for hybridisation assays appears to be unsuitable, especially for patients with HBeAg-negative CHB. Furthermore, the diagnosis of inactive HBsAg carrier should never be based on a single blood determination and this principle should apply throughout all phases of chronic HBV infection. In this context, it is important to consider the clinical spectrum of HBeAg-negative CHB. Three patterns have been recognised: (i) recurrent hepatitis B exacerbations with periods of biochemical and virologic remission; (ii) unremitting chronic hepatitis B; and (iii) unremitting chronic hepatitis B with acute exacerbations (Figure 1).

Several studies have shown that when using a serum HBV DNA cut-off of 10^5 copies/mL, patients with a measurement above this threshold can be safely excluded from being inactive HBsAg carriers. While an HBV DNA measurement above 10^5 copies/mL may be useful for reliably excluding inactive HBsAg carriers, a measurement below 10^5 copies/mL is less useful when differentiating HBeAg-negative CHB from inactive carriage. This is especially so if the diagnosis is based on a single determination. Almost half of HBeAg-negative CHB cases would be excluded by a single time point measurement using this threshold. Only one third of HBeAg-negative CHB patients have HBV DNA levels persistently above 10^5 copies/mL. Thus, a decision based on measurement of HBV DNA and ALT at a single time point may be misleading. It is reported that even if HBV DNA measurements are taken at three different time points, a threshold of 10^5 copies/mL could miss 30% of HBeAg-negative patients. An HBV DNA level of 10^5 copies/mL may therefore be a better threshold level. One study has reported that a cut-off value of 3 × 10^5 copies/mL would differentiate inactive HBsAg carriers from HBeAg-negative chronic hepatitis B. However, these data were not confirmed by Chu and colleagues who reported that this cut-off value would misclassify 7% of inactive HBsAg carriers and, more importantly, 30% of patients with HBeAg-negative chronic hepatitis B.
The clinical significance of low levels of HBV DNA is less clear; however, studies have confirmed that these patients may still have progressive liver disease although disease progression in such patients would be expected to be slower than in patients with high HBV DNA levels.

The true diagnosis and thus differentiation of HBeAg-negative CHB from the inactive carrier state is important, particularly given that patients with HBeAg-negative CHB are likely to have been infected for a longer duration and are thus more likely to have cirrhosis. Once HBeAg-negative CHB is diagnosed, the pros and cons of a finite treatment course with pegylated interferons versus prolonged treatment with a nucleos(t)ide analogue should be discussed with the patient, and the type of treatment the patient is going to receive should be a joint decision of the treating physician and the patient. It should be noted that the majority of patients will relapse if treatment is withdrawn and indefinite treatment is likely.

When should treatment in HBeAg-negative CHB be commenced? Are there any data to suggest which patients would respond better to treatment with nucleos(t)ide analogues? Are patients with a particular HBV genotype, ALT level, or HBV DNA viral load more likely to respond to treatment? In contrast to the situation with interferon-based treatment regimes, nucleos(t)ide analogues are generally effective irrespective of HBV genotype, although according to one study patients infected with HBV genotype A may be more prone to develop lamivudine resistance than those with genotype D infection. Studies investigating predictive factors of response to treatment with nucleos(t)ide analogues in patients with HBeAg-negative CHB are scarce. One recent study suggests that baseline factors predicting response to treatment in HBeAg-negative CHB are elevated ALT, low HBV DNA, female gender, and younger age. This suggests that antiviral treatment may best be commenced at the time of a biochemical flare when these patients would also be expected to have low levels of HBV DNA.

In this case the patient was treated with lamivudine at a time when it was the only available nucleos(t)ide analogue. A concern with nucleos(t)ide analogue monotherapy, and with lamivudine in particular, is the development of resistance to the agent used. Therefore, it is recommended that HBV DNA levels be tested every 3–6 months. The importance of compliance should be emphasised. A factor gaining increasing importance in the treatment of CHB with nucleos(t)ide analogues is the on-treatment predictors of response. HBV DNA levels after six months on therapy (or at week 48 for adefovir) appear to predict response and, more importantly, those patients who are likely to have viral breakthrough or risk the emergence of resistant mutants. Patients whose HBV DNA level remains <1% in treatment-naïve patients at year 2. Telbivudine resistance is associated with the M204I mutation, part of the YMDD locus, this indicates that if these mutations appear during prior lamivudine therapy, cross-resistance to telbivudine will occur.

Finally, an important question is how long treatment with nucleos(t)ide analogues should be continued. The situation is clearer in HBeAg-positive CHB; HBeAg seroconversion is a well-established endpoint and treatment can be discontinued after a consolidation phase of at least six months following seroconversion. The situation is less clear in HBeAg-negative CHB. Discontinuation of nucleos(t)ide analogues or interferon-based therapy is, in general, associated with viral rebound. One reasonable approach would be to continue antiviral therapy until the definite endpoint of HBsAg loss (± HBsAg seroconversion) is reached. The problem with this solid endpoint is that very few patients will achieve it. If it is clear that prolonged, if not indefinite, treatment is therefore necessary. The effect of discontinuation of treatment in patients with persistent undetectable HBV DNA by PCR after five years of treatment with adefovir dipivoxil has recently been reported. Although the results of that study appear promising, the patient cohort was relatively small and further follow-up and confirmation is needed before any recommendation can be made. Until further evidence is available, the majority of patients with HBeAg-negative will require long-term therapy.

The above-described patient responded very well to treatment with lamivudine. After five years of treatment she continues to be HBV DNA-negative by a PCR-based assay and has normal aminotransferase levels. During the five years of treatment she was seen mostly at three-month intervals, especially after the first year of treatment. At each visit, blood was drawn for haematology, biochemistry, and for HBV DNA determination.

However, most patients are not as lucky as ours. Thus, viral breakthrough indicative of lamivudine resistance would be an expected finding with the first year of treatment. At each visit, blood was drawn for haematology, biochemistry, and for HBV DNA determination. PCR-based assay and has normal aminotransferase levels. During the five years of treatment she was seen mostly at three-month intervals, especially after any recommendation can be made. Until further evidence is available, the majority of patients will relapse if treatment is withdrawn and indefinite treatment is likely.

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However, most patients are not as lucky as ours. Thus, viral breakthrough indicative of lamivudine resistance would be an expected finding with lamivudine treatment in approximately 70% of patients by four years. Lamivudine compromises future treatment opportunities. Accumulating evidence suggests that not switching to adefovir but rather adding adefovir to continuing lamivudine treatment reduces the risk of adefovir resistance, and that adefovir should be started as early as possible, i.e., once genotypic resistance has been detected without waiting for clinical breakthrough to occur. Data for entecavir indicate that higher doses (1 mg qd) are required in patients with lamivudine resistance, and that these patients are more susceptible to treatment-emergent resistance to entecavir (with virological rebound due to entecavir resistance in 15–19% at year 3 vs <1% in treatment-naïve patients at year 2). Tليفiduvir resistance is associated with the M204I mutation, part of the YMDD locus, this indicates that if these mutations appear during prior lamivudine therapy, cross-resistance to tليفiduvir will occur.

### References

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