

Antiviral treatment for chronic hepatitis B virus infection – immune modulation or viral suppression?

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ABSTRACT

The availability of nucleoside analogues has broadened treatment options for chronic hepatitis B virus (HBV) infection. Registered treatment for chronic hepatitis B currently consists of (pegylated) interferon, lamivudine and adefovir, while entecavir is expected to be licensed in the short term. Treatment is generally recommended for patients with high serum HBV DNA and elevated ALAT, indicating the host's immune response against HBV. Induction of an HBV-specific immune response seems crucial for persistent control of HBV infection. Currently available treatment strategies can be differentiated into those that provide sustained off-treatment response and those that provide therapy maintained response. A finite treatment course with immunomodulatory agents (interferon-based therapy) results in sustained response in about one third of patients, while nucleoside analogue treatment generally requires indefinite therapy without a clear stopping point. Since nucleoside analogues are well tolerated, prolonged therapy is feasible, but a major drawback is the considerable risk of developing antiviral resistance, which occurs most frequently in lamivudine-treated patients and to a lesser extent during adefovir or entecavir therapy. In our opinion, treatment with peginterferon should therefore be considered first-line therapy in eligible patients with a high likelihood of response based on serum HBV DNA, ALAT and HBV genotype. Patients not responding to PEG-IFN therapy or not eligible for peginterferon therapy should be treated with nucleos(t)ide analogues.

KEYWORDS

Adefovir, interferon, lamivudine, nucleoside analogues, peginterferon

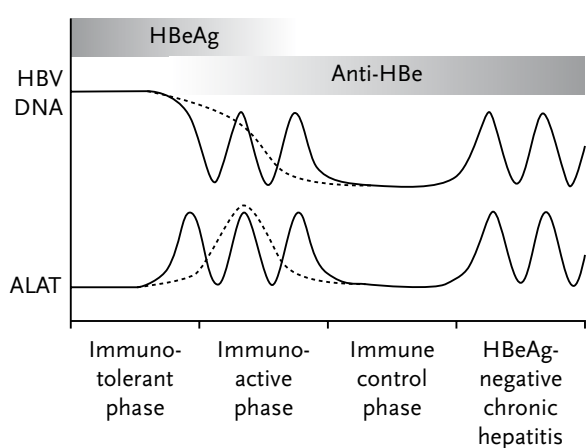
INTRODUCTION

Worldwide more than two billion people have been infected with hepatitis B virus (HBV) and chronic HBV infection affects about 400 million people.^{1,2} It is estimated that more than 500,000 people die annually due to HBV-associated liver disease, largely because of cirrhosis and/or hepatocellular carcinoma.³ Despite the availability of safe and effective vaccines for more than two decades, HBV infection is still a global health problem. The approach to the treatment of chronic HBV infection has dramatically changed over the past decade and the current availability of a number of antiviral drugs adds to the complexity of management of chronic HBV. This paper provides a practical review of available treatment options to guide decisions on optimal therapy based on both patient and treatment characteristics. The main focus will be on deciding between a finite course of immunomodulatory therapy with (pegylated) interferon (IFN) or prolonged viral suppression with nucleoside analogues.

Natural history

In adults, infection with HBV is usually asymptomatic and results in chronic infection in <5% of patients.³ Infection at younger age is associated with a higher risk of chronic infection, up to 90% in the setting of perinatal transmission.³ Patients can present with chronic HBV in one of four phases of infection (*figure 1*).⁴ In the immunotolerant phase of infection, hepatitis B surface

Figure 1. Natural history of chronic hepatitis B infection



This figure shows the phases in chronic hepatitis B infection. Patients can be categorised in one of these four phases depending on serum HBV DNA and ALAT, and the presence or absence of HBeAg and anti-HBe.

antigen (HBsAg) and hepatitis B e antigen (HBeAg) are present and HBV DNA levels are high, $>1.0 \times 10^5$ copies per millilitre (c/ml). Hepatic inflammation is mild with normal or minimally elevated serum alanine aminotransferase (ALAT) levels and minimal necroinflammation on liver histology. In the immuno-active phase, HBsAg, HBeAg and high HBV DNA are still present, while an active immune response results in hepatic inflammation with elevation of serum ALAT. In the immune-clearance phase HBeAg is present and HBV DNA levels can be high or fluctuating. Liver inflammation is present with elevated serum ALAT and active inflammation on liver histology; loss of HBeAg and seroconversion to anti-HBe can occur. The immune-control phase follows HBeAg seroconversion. In this phase hepatic inflammation is minimal and HBV DNA levels are low due to continuous host immune response. This phase of infection is also referred to as the 'inactive carrier state'. In an increasing number of patients with HBeAg-negative HBV, biochemical and histological activity recur and HBV DNA levels are high, resulting in HBeAg-negative chronic hepatitis. These patients often originate from the Mediterranean basin, and are infected with hepatitis B variants that hamper the production of HBeAg. The most commonly described mutation is a G to A transition at position 1896 of the precore region. Three major patterns of HBeAg-negative HBV can be distinguished: a recurrent form with exacerbations and periods of remission (45%), an unremitting form (36%), and an unremitting form with acute exacerbations (20%).⁵ Despite the occurrence of HBeAg-negative HBV, HBeAg seroconversion is still usually associated with improved long-term outcome and therefore considered an important event in the natural course of chronic HBV.⁶

Spontaneous HBeAg seroconversion occurs in 8 to 15% of patients in Western countries.³ Before achieving HBeAg seroconversion many patients have episodes of acute exacerbation.^{7,8} The chance of HBeAg seroconversion during acute exacerbation increases with increasing serum ALAT levels, to 45% in patients with ALAT >5 times the upper limit of normal (ULN).^{9,10}

Progression to cirrhosis

The overall annual incidence of progression to cirrhosis in chronic HBV-infected patients is about 6%, with a cumulative five-year probability of 20%.¹¹ In HBeAg-positive patients the annual incidence of progression to cirrhosis is 2 to 5%.³ Factors associated with an increased rate of progression to cirrhosis include high serum HBV DNA, coinfection with hepatitis C virus (HCV), hepatitis D virus (HDV) or human immunodeficiency virus (HIV), recurrent episodes of acute exacerbation and severe necroinflammation at diagnosis.^{3,12-14} The probability of survival five years after diagnosis of cirrhosis is 84%.¹⁵ Hepatic decompensation occurs at an annual rate of about 3% in cirrhotic patients, with a five-year cumulative incidence of 16%.³ Development of decompensated cirrhosis is associated with survival of only 35% at five years.¹⁶

Hepatocellular carcinoma

The development of hepatocellular carcinoma (HCC) is a major global health problem.¹⁷ Cirrhosis predisposes to HCC and the majority of patients with HCC have underlying cirrhosis (80 to 90%).¹⁸ The annual incidence of HCC in European patients with chronic hepatitis B is about 2.2% in patients with compensated cirrhosis, with a five-year cumulative incidence of about 10%.¹⁸ In Asians the incidence of HCC is higher with an annual rate of 3.2% in patients with cirrhosis and a five-year cumulative incidence of 15%.¹⁸ Predictors of the occurrence of HCC in cirrhotic patients include older age, male sex, sustained activity of liver disease, high HBV DNA level, HBeAg positivity, coinfection with HCV or HIV and alcohol abuse.¹⁸⁻²¹ Screening for HCC, with monitoring of α -fetoprotein levels and six-monthly radiographic examination should be considered for patients at increased risk of developing HCC.²²

Hepatitis B virus genotypes

Hepatitis B virus has been classified into eight genotypes (A-H) (table 1).²³⁻²⁵ Genotypes A and D are most frequently observed in Europe and North America, while genotypes B and C are prevalent in Asia. Compared with genotype C, genotype B is associated with spontaneous HBeAg seroconversion at younger age, less active liver disease, a slower rate of progression to cirrhosis and less frequent development of HCC.²⁶⁻²⁸ Findings on the relationship of other genotypes with clinical outcome are contradictory.^{29,30} HBV genotype has been reported to be associated with

response to (pegylated) interferon treatment. HBeAg seroconversion was found to occur more often in patients with genotype A and B than in those with genotype C and D.³¹⁻³³ Genotype B seems to have a better virological response to lamivudine than genotype C.³⁴

Hepatitis B virus immunopathogenesis

Hepatitis B virus specific T-cell response plays a crucial role in control of viral infection. A vigorous, polyclonal and multispecific peripheral blood T-cell response can be observed in patients with acute self-limiting HBV.^{35,36} Activated HBV-specific helper and cytotoxic T-cells are still present several years after recovery from acute hepatitis B and seem to be maintained by continuous stimulation by minute amounts of persisting virus. Therefore, resolution of disease does not imply complete eradication of infection but merely reflects the capacity of HBV-specific T-cells to persistently control HBV infection.^{37,38} Viral persistence is believed to be associated with functional tolerance of helper

T-lymphocytes and cytotoxic T-lymphocytes to HBV.³⁹ In chronic HBV-infected patients levels of HBV-specific helper T-cells and cytotoxic T-lymphocytes are generally very low or undetectable.³⁵

MANAGEMENT OF CHRONIC HEPATITIS B VIRUS INFECTION

Patients eligible for antiviral treatment

Antiviral treatment is, in general, not recommended for patients with acute hepatitis B, since the outcome of acute hepatitis B is good in the vast majority of immunocompetent adult patients. For HBeAg-positive patients, treatment is recommended for chronically infected patients with HBV DNA $>10^5$ c/ml and persistence of elevated ALAT levels (more than twice the upper limit of normal) over a three to six month period (table 2). An HBV DNA level of 10^4 c/ml should be used for HBeAg-

Table 1. Geographical distribution of hepatitis B virus genotypes

Genotype	Subtypes	Geographical distribution
A	adw2, ayw1	North-Western Europe, Spain, Poland, USA, Central Africa, India, Brazil
B	adw2, ayw1	Southeast Asia, Taiwan, Japan, Indonesia, China, Hong Kong, Vietnam, Thailand
C	adw2, adrq+, adrq-, ayr	Far East Asia, Taiwan, Japan, Korea, China, Hong Kong, Thailand, Indonesia, Polynesia, Solomon Islands, Vietnam, India, Australia, USA, Brazil
D	ayw2, ayw3	Mediterranean area, Albania, Middle East, Turkey, Iran, India, Spain, Czech, Russia, USA, Brazil, Solomon Islands
E	ayw4	West Africa
F	adw4q-, adw2, ayw4	Central and South America, Bolivia, Venezuela, Argentina, Brazil, Polynesia, Alaska
G	adw2	France, Germany, USA
H	adw4	Central and South America

This table shows the association of eight hepatitis B virus genotypes with various subtypes and geographic distribution according to genotype.

Table 2. Management strategies in chronic hepatitis B

Stage of disease	HBeAg status	ALAT	HBV DNA (c/ml)	Management strategy
Compensated liver disease	HBeAg positive	$\geq 2x$ ULN	$\geq 1.0 \times 10^5$	Antiviral treatment indicated (PEG-IFN or nucleos(t)ide analogue therapy)
		$< 2x$ ULN	$\geq 1.0 \times 10^5$	3 monthly monitoring, consider liver biopsy (consider treatment in case of active necroinflammation)
		$< 2x$ ULN	$< 1.0 \times 10^5$	3 monthly monitoring
	HBeAg negative	$\geq 2x$ ULN	$< 1.0 \times 10^5$	Exclude other causes of hepatitis, consider liver biopsy
		$\geq 2x$ ULN	$\geq 1.0 \times 10^4$	Antiviral treatment indicated (PEG-IFN or nucleos(t)ide analogue therapy)
		$< 2x$ ULN	$\geq 1.0 \times 10^4$	3-6 monthly monitoring, consider liver biopsy (consider treatment in case of active necroinflammation)
Decompensated liver disease	HBeAg positive	$< 2x$ ULN	$< 1.0 \times 10^4$	6-12 monthly monitoring
		$\geq 2x$ ULN	$< 1.0 \times 10^4$	Exclude other causes of hepatitis, consider liver biopsy
	HBeAg negative	Any level	Positive by PCR (> 300)	Antiviral treatment indicated (nucleos(t)ide analogue therapy)
		Any level	Positive by PCR (> 300)	Antiviral treatment indicated (nucleos(t)ide analogue therapy)

This table shows management strategies for chronic hepatitis B infected patients based on the stage of liver disease, HBeAg status, HBV DNA level and serum alanine aminotransferase (ALAT). For patients with no treatment indication at this moment, monitoring of these variables at various intervals is recommended. ULN = upper limit of normal; PCR = polymerase chain reaction.

negative patients, since this level was found to differentiate patients from having HBeAg-negative chronic hepatitis or being inactive carriers.⁴⁰ In HBeAg-negative patients with HBV DNA $>10^4$ or HBeAg-positive patients with HBV DNA $>10^5$ c/ml, and presence of normal ALAT levels, a liver biopsy may be considered to guide decisions on antiviral therapy.⁴¹ In case of active necroinflammation, antiviral treatment can be considered. In patients with histological or clinical evidence of advanced fibrosis or cirrhosis, treatment with lamivudine has shown to reduce progression to decompensated liver disease and hepatocellular carcinoma.⁴² Since serum HBV DNA has become increasingly important in the management of chronic HBV, use of standardised assays for quantification of HBV DNA is essential.

Patients who are currently not candidates for treatment should be monitored, as their condition may run a fluctuating course and treatment may be needed on future examinations (table 2). For HBeAg-positive patients with high serum HBV DNA but normal ALAT levels, monitoring ALAT with three monthly intervals is recommended, with more frequent monitoring when ALAT levels become elevated. Testing for liver chemistry should be performed every six to twelve months to account for reactivation of liver disease in HBeAg-negative patients with low serum HBV DNA and normal ALAT levels.⁴³

Goals of therapy

Sustained viral suppression is the key to reduce hepatic necroinflammation and progression of liver fibrosis. Since elimination of HBV infection (HBsAg seroconversion) can only be achieved in a small proportion of patients with currently available antiviral agents, permanent suppression of HBV is the primary goal of treatment. Further, seroconversion to anti-HBe should be pursued in HBeAg-positive patients since this is associated with improved outcome.^{44,45}

Definition of response to antiviral treatment

Response to antiviral treatment can be defined as sustained off-therapy or therapy-maintained response. Biochemical response is defined as decrease in serum ALAT to within the normal range. A virological response is defined as HBV DNA $<10^5$ c/ml or HBV DNA negativity by sensitive molecular assays, and loss of HBeAg in previously positive patients.³ Histological response is best defined as a two-point decrease in necroinflammatory score with no worsening of fibrosis. Complete response is defined as loss of HBsAg with appearance of anti-HBs.

Treatment of chronic hepatitis B

Two major types of antiviral drugs are being used for the treatment of chronic HBV: drugs that directly interfere with virus replication and drugs that modulate the HBV-specific immune response. Nucleoside and nucleotide analogues, such as lamivudine, adefovir and entecavir, directly inhibit reverse

transcriptase and thereby impair viral replication. Interferon (IFN) has marked immunomodulatory, but less pronounced direct antiviral effects. Registered treatment for chronic HBV in most countries currently consists of interferon-alpha, lamivudine, adefovir, peginterferon- α -2a and entecavir, of which the last two have recently been approved. Approval of entecavir for the treatment of chronic HBV in Europe is expected on the short term. Advantages and limitations of, and response to a one-year course of treatment with these antiviral agents, as well as factors influencing likelihood of response, are shown in tables 3 and 4.

IMMUNOMODULATORY DRUGS

Pegylated interferon- α

Interferon-alpha (IFN- α) was licensed for the treatment of chronic hepatitis B in most countries in the early 1990s. Interferons are naturally occurring cytokines with immunomodulatory, antiproliferative and antiviral properties.⁴⁶

In HBeAg-positive patients IFN- α results in loss of HBeAg in 25 to 40% of patients.^{44,47-52} The majority of patients have a durable response; reactivation occurs in 10 to 20% of patients.^{44,53,54} Standard IFN- α induced responses are less durable in HBeAg-negative chronic HBV, with sustained response in 10 to 47% (average 24%) at 12 months after cessation of therapy.^{55,59} Long-term follow-up studies showed better overall survival and lower incidence of hepatic decompensation and HCC in responders to IFN- α therapy.^{44,45,54,60}

The addition of a polyethylene glycol (PEG) molecule to IFN significantly prolongs half-life and results in more sustained IFN activity. Two pegylated IFNs have been studied for the treatment of HBV, a large branched 40kDa PEG linked to IFN α -2a (peginterferon α -2a) and a small linear 12kDa PEG linked to IFN α -2b (peginterferon α -2b).⁶¹ Both these interferons were initially investigated for the treatment of chronic hepatitis C infection and have shown similar tolerability and higher rates of sustained viral response compared with conventional IFN.^{62,63} Peginterferon-alpha-2a (PEG-IFN α -2a) has recently been registered for the treatment of chronic HBV in Europe and the United States and should be given by subcutaneous injection once weekly for 48 weeks in a dosage of 180 microgram in both HBeAg-positive and HBeAg-negative patients. Results of treatment with PEG-IFN during shorter periods are very limited. Peginterferon-alpha-2b (PEG-IFN α -2b) will only be registered in specific east-Asian countries.

In HBeAg-positive patients treatment with PEG-IFN was found superior to conventional IFN, with loss of HBeAg in 35% and seroconversion to anti-HBe in 29 to 32% of patients.^{32,64,66} Long-term follow-up of patients treated with PEG-IFN and lamivudine combination therapy showed

Table 3. Comparison of drugs approved for the treatment of chronic hepatitis B

Treatment	Advantage	Disadvantage	HBeAg positive		HBeAg negative	
			HBeAg seroconversion		HBV DNA negativity	
			EOT	EOFU	EOT	EOFU
Alpha-interferon	Finite treatment course No drug resistance	Frequent subcutaneous injection Frequent adverse events Contraindicated in advanced cirrhosis High costs	35% (44, 47-51)*	30% (44, 47-51, 53, 65)	60% (55-59, 119, 120)*	35% (55-59)*
Peginterferon	Finite treatment course Weekly dosage interval No drug resistance	Subcutaneous injection Frequent adverse events Contraindicated in advanced cirrhosis High costs	40% (32, 64-66)*	35% (32, 64-67)*	63% (68)*	19% (68)*
Lamivudine	Oral administration Good tolerability Low costs	Long duration of treatment High incidence of antiviral resistance	19% (74-78)*	12% (67, 83, 84)*	65% (68, 85, 87)*	10% (68, 86)*
Adefovir	Oral administration Low incidence of antiviral resistance	Long duration of treatment Weak antiviral effect Renal toxicity	12% (93)*	NA	51% (95)*	NA
Entecavir	Oral administration Strongest HBV inhibitor Good tolerability Low incidence of antiviral resistance	Long duration of treatment High costs	21% (102)*	NA	90% (103)*	NA

This table shows mean response rates (HBeAg seroconversion for HBeAg-positive patients and undetectable HBV DNA for HBeAg-negative patients) at the end of treatment (EOT) with various antiviral drugs for 48 to 52 weeks and at the end of follow-up (EOFU) (NA = data not available). Response to therapy is less durable in HBeAg-negative patients compared with HBeAg-positive patients. Further, while (PEG-)IFN associated responses are generally durable, relapse occurs in a large proportion of nucleos(t)ide analogue treated patients after discontinuation of therapy. *References.

Table 4. Predictors of response to antiviral therapy in HBeAg-positive patients

Treatment	Decreased likelihood of response	Increased likelihood of response
(Peg)interferon	Baseline ALAT $\leq 2 \times \text{ULN}^{119}$ Baseline HBV DNA $> 10^9 \text{ c/ml}^{64}$ Genotype C or D ³¹⁻³³ HIV coinfection ¹²¹	Baseline ALAT $> 2 \times \text{ULN}^{119}$ Baseline HBV DNA $\leq 10^9 \text{ c/ml}^{64}$ Genotype A or B ³¹⁻³³
Nucleoside analogues	Baseline ALAT $\leq 2 \times \text{ULN}^{81}$ HAI $0-9^{81}$	Baseline ALAT $> 2 \times \text{ULN}^{81}$ HAI $\geq 10^{81}$

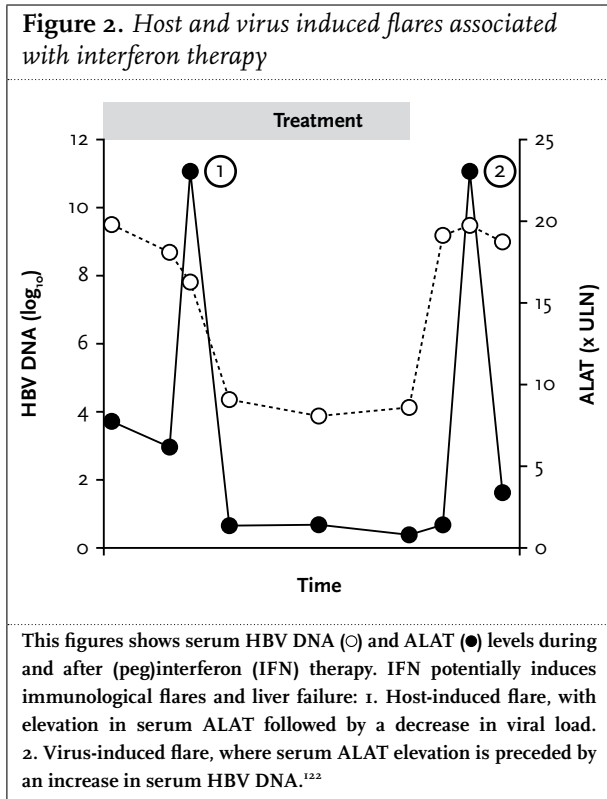
This table shows baseline factors influencing likelihood of response to antiviral therapy in HBeAg-positive patients. ALAT = alanine aminotransferase; HBV = hepatitis B virus; ULN = upper limit of normal; HAI = histological activity index.

durable response at 72 weeks post-treatment in over 80% of responders.⁶⁷ In HBeAg-negative HBV only one large randomised controlled trial using PEG-IFN has been conducted so far.⁶⁸ At the end of follow-up, a combined response, with suppression of serum HBV DNA below 10^4 c/ml and normalisation of ALAT, was observed in 36% of patients. HBsAg seroconversion occurs in 3 to 7% of PEG-IFN treated patients, which represents 10 to 20% of virological responders.^{32,64,68} HBV genotype appears to predict response to PEG-IFN, with a higher probability of HBeAg loss and HBsAg loss for patients with genotype A (47 and 14%) and B (44 and 9%) compared with genotype C (28% and 3%) and D (25 and 2%).^{32,65,69} Addition of a nucleoside analogue to

PEG-IFN therapy does not increase response rates in either HBeAg-positive or HBeAg-negative patients, as has earlier been shown in conventional IFN therapy.^{32,64,68,70}

Interferon can have several side effects including influenza-like symptoms, fatigue, headache, myalgia, gastrointestinal symptoms (nausea, anorexia, weight loss), alopecia and local reaction at the injection site. These side effects are frequently observed, but rarely lead to discontinuation of treatment. More serious adverse events such as myelosuppression, neuropsychiatric symptoms (irritability, depression and insomnia), neurological symptoms and thyroid dysfunction may require dose reduction or discontinuation.^{71,72} Use of PEG-IFN is not recommended in advanced liver disease

since it may potentially precipitate immunological flares and liver failure in these patients (figure 2).⁷³ Adverse events observed during treatment with PEG-IFN are similar to those observed with conventional IFN. The proportion of patients requiring discontinuation of treatment for safety reasons was comparable for PEG-IFN and standard IFN.



levels detectable by non-PCR assays and seroconversion from HBeAg to anti-HBe has been achieved. However, lamivudine-induced HBeAg seroconversion is significantly less durable than HBeAg seroconversion following IFN-containing therapies.⁸² Data on durability of response to lamivudine are limited, HBeAg seroconversion has been reported to be durable in 50 to 77% of patients.^{83,84} Prolonged duration of ongoing lamivudine therapy after HBeAg seroconversion and low pretreatment HBV DNA seem to be associated with decreased relapse rates.⁸³

In HBeAg-negative patients serum HBV DNA was undetectable by PCR assay in 68 to 73% of patients after one year of lamivudine therapy. At this time point 73 to 96% of patients showed biochemical response.^{68,85,86} However, relapse occurred in 66 to 85% of patients after discontinuation of treatment. In patients treated continuously over one year, response rates progressively declined to about 67% after two years, 60% after three years and 39% after four years.^{85,87,88}

Prolonged lamivudine treatment can be used to prevent adverse clinical outcome in patients with advanced liver disease (bridging fibrosis or cirrhosis). Disease progression, defined as a two-point increase in Child-Turcotte-Pugh score, and development of HCC were found to be significantly decreased in lamivudine treated patients compared with untreated controls.⁴²

The major drawback of lamivudine, which significantly limits its use as first-line therapy, is the high rate of occurrence of viral resistance. The majority of patients with virological breakthrough show mutations in the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the polymerase gene.⁸⁸ The most important mutation is a substitution of valine or isoleucine for methionine at position 204 (rtM204V/I).⁸⁹ In many patients this is accompanied by a second mutation substituting methionine for leucine in an upstream region (rtL180M). Lamivudine resistance is more likely to occur in patients with high baseline serum HBV DNA levels and patients with HBV DNA >10³ c/ml after six months of treatment.⁹⁰ The frequency of resistance increases with the duration of treatment from 24% at one year to 38% at two years, 50% at three years and 67% at four years.^{79,80,87} The emergence of lamivudine-resistant mutants is usually associated with an increase in serum HBV DNA and ALAT, and selection of YMDD variants has been associated with worsening of liver histology.⁹¹

Adefovir dipivoxil

Adefovir dipivoxil is the oral prodrug of adefovir and has activity against both wild-type and lamivudine-resistant HBV.⁹² Adefovir is a nucleotide analogue of adenosine monophosphate and acts as a competitive inhibitor and chain terminator of viral replication. Adefovir at the dose of 10 mg daily is well tolerated and has a good safety profile.⁹³

NUCLEOS(T)IDE ANALOGUES

Lamivudine

Lamivudine was the first nucleoside analogue licensed for the treatment of chronic HBV. Lamivudine is a cytosine analogue and inhibits reverse transcriptase by competing for incorporation into growing DNA chains causing chain termination. Lamivudine can be taken orally in a dosage of 100 mg daily, is generally well tolerated and has an excellent safety profile.

HBeAg seroconversion with HBV DNA <10⁵ c/ml occurs in 16 to 22% of patients by one year compared with 4 to 13% of untreated controls.^{74,79} Higher cumulative HBeAg-seroconversion rates were observed with increased duration of lamivudine treatment, with 29% at two years, 40% at three years, and 47% at four years of therapy.^{76,79,80} Reduction of serum HBV DNA occurs in 98% of patients.⁷⁵ Elevated ALAT >2 x ULN was found to be the best predictor of response to lamivudine.⁸¹ Lamivudine treatment may be discontinued if HBV DNA is suppressed below

In HBeAg-positive patients, serum HBV DNA levels $<10^3$ c/ml and normalisation of ALAT were observed in 21 and 48% of treated patients, compared with 0 and 16% of untreated controls after one year of adefovir therapy, respectively. HBeAg seroconversion occurred in 12% of patients receiving adefovir compared with 6% in the placebo group.⁹³ Continued adefovir therapy over one year increased rates of HBeAg seroconversion to 29% after two years and 43% after three years. A similar increase in the proportion of patients with HBV DNA $<10^3$ c/ml was observed, to 45 and 56% of patients after 96 and 144 weeks, respectively.⁹⁴

In HBeAg-negative patients, treatment with adefovir for one year resulted in serum HBV DNA $<10^3$ c/ml and normalisation of ALAT in 51 and 72% of treated patients, compared with 0 and 29% of untreated controls.⁹⁵ The percentage of HBeAg-negative patients with HBV DNA $<10^3$ c/ml was 71% at two years and 67% at five years, and ALAT normalised in 73 and 69%, respectively.^{96,97} Prolonged adefovir therapy significantly improved liver histology compared with baseline in up to 75 to 80% of patients after five years.⁹⁶ Response to adefovir is generally not durable after discontinuation of treatment.^{95,97}

Resistance to adefovir is less common and occurs later in the course of HBV treatment compared with lamivudine. To date, mutations in the polymerase gene that have been confirmed to confer resistance to adefovir include rtN236T and rtA181V.⁹⁸ The rtN236T mutation occurs most frequently and is associated with the selection of a novel asparagine to threonine substitution at residue rt236 in the domain D of the HBV polymerase.⁹⁷ The rtA181V mutation involves a substitution of alanine by valine or threonine at position rt181 of the B domain of the HBV polymerase. The cumulative probability of adefovir resistance is 0 and 28% at one and five years, respectively.⁹⁶

Entecavir

Entecavir is a guanosine analogue and a potent inhibitor of the HBV polymerase. Entecavir has activity against both wild-type and lamivudine resistant HBV. Entecavir can be taken orally, is well tolerated and safe at daily dosages up to 1 mg.^{99,100} Entecavir has recently been approved by the FDA for the treatment of chronic hepatitis B and should be given in a dosage of 0.5 mg daily in nucleoside analogue naive patients and 1 mg in lamivudine-refractory patients.^{100,101}

In both HBeAg-positive and HBeAg-negative naive patients, one year of entecavir (0.5 mg daily) was found to be superior to lamivudine therapy in reducing serum HBV DNA (6.9 vs 5.4 log for HBeAg-positive and 5.0 vs 4.5 log for HBeAg-negative patients, respectively) and histological improvement.^{102,103} HBeAg seroconversion, HBV DNA negativity by PCR assay and normalisation of ALAT were observed in 21, 67 and 68% of HBeAg-positive patients treated with entecavir for 48 weeks, respectively.¹⁰² Prolonging entecavir therapy to 96 weeks resulted in HBeAg

seroconversion in 31% and HBV DNA $<10^2$ c/ml in 80% of patients, respectively.¹⁰⁴ In HBeAg-negative patients HBV DNA negativity by PCR assay occurred in 90% of patients, while 78% of patients had normalisation of ALAT at week 48.¹⁰³ In lamivudine-refractory patients treatment with entecavir 1 mg daily was superior to 0.5 mg daily, and resulted in HBeAg seroconversion in 4%, HBV DNA $<10^2$ c/ml in 26% and normalisation of ALAT in 68% of patients, respectively.¹⁰¹ Based on these results, entecavir appears to be a stronger inhibitor of HBV than either lamivudine or adefovir.

Entecavir resistance requires pre-existing lamivudine resistance and additional changes at residue rtT184, rtS202 or rtM250 of the HBV reverse transcriptase.¹⁰⁵ Resistance to entecavir was not observed in nucleoside analogue naive patients treated with entecavir for 48 weeks or 96 weeks.¹⁰⁶⁻¹⁰⁸ In lamivudine-refractory HBV resistance to entecavir has not been described after one year of therapy. However, changes at the rtT184 and/or rtS202 residue were observed in 10% of patients after two years of entecavir treatment.¹⁰⁹

NEW DRUGS

Emtricitabine is structurally similar to lamivudine (3TC) and has potent antiviral activity against HBV and human immunodeficiency virus (HIV). Seroconversion from HBeAg to anti-HBe can be observed in 12 to 23% of patients after 48 weeks, increasing to 33% after 96 weeks of treatment.^{104,110} In HBeAg-negative patients serum HBV DNA was $<10^4$ c/ml in 76 and 71% of patients after 48 weeks and 96 weeks of treatment, respectively.¹⁰⁴ Mutations associated with resistance to emtricitabine were observed in 12 and 18% of patients after 48 weeks and 96 weeks of treatment, respectively.¹⁰⁴ With the advent of newer antiviral agents with significantly lower risk of antiviral resistance, emtricitabine will possibly have a minor role as monotherapy for HBV.

Telbivudine is an L-nucleoside analogue, which is more potent than lamivudine in suppressing HBV DNA.¹¹¹ Serum HBV DNA was undetectable by PCR assay in 61% of patients at week 52, while HBeAg seroconversion occurred in 31% of patients. Combination of telbivudine with lamivudine did not result in increased response rates. Resistance to telbivudine emerged in 5% of patients after one year of therapy. Ongoing phase III trials will help determine the role of telbivudine in the treatment of chronic HBV.

Tenofovir disoproxil fumarate is an acyclic nucleotide analogue and has been approved for the treatment of HIV infection. Dosage of tenofovir for hepatitis B infection is 300 mg daily. Tenofovir seems more potent in suppression of HBV DNA than adefovir, with HBV DNA undetectable by PCR assay in all patients treated with tenofovir compared with 44% of patients treated with adefovir at week 48.¹¹² Currently, randomised controlled trials comparing tenofovir and adefovir are being performed.

ANTIVIRAL RESISTANCE

The highest incidence antiviral resistance has been reported during lamivudine treatment,⁸⁰ while resistance to adefovir and entecavir is less common.^{96,105} During nucleoside analogue treatment, close monitoring for antiviral resistance is advised, since hepatitis flares have been reported following lamivudine resistance. Antiviral resistance should be suspected if rebound of viral replication (1 log₁₀ increase in serum HBV DNA) occurs in a fully compliant patient after initial response, antiviral resistance testing should then be considered (figure 3). It is still being debated whether combination nucleoside analogue treatment should be given, as for HIV infection, or subsequent introduction in case of nonresponse or resistance should be used. Prolonged combination therapy after emergence of antiviral resistance does not seem beneficial.¹¹³ However, whether a shorter overlap period of combination therapy is preferable in patients with advanced liver disease before discontinuing initial treatment has not been assessed. Sequential monotherapy may facilitate resistance to other drugs and may ultimately lead to multiresistance.¹⁰⁹ Following that rationale, lamivudine treatment may negatively influence future treatment options due to the high incidence of antiviral resistance. Furthermore, a recent study showed decreased responsiveness of lamivudine-resistant patients to a course of PEG-IFN.¹¹⁴ Using lamivudine as initial therapy is therefore highly questionable. Currently adefovir is preferable as first-line nucleoside analogue therapy

because of its favourable resistance profile. Entecavir and tenofovir seem to be the drugs with most potent anti-HBV activity and lowest rate of antiviral resistance discovered to date and may become the new standard in nucleos(t)ide analogue treatment for chronic hepatitis B.

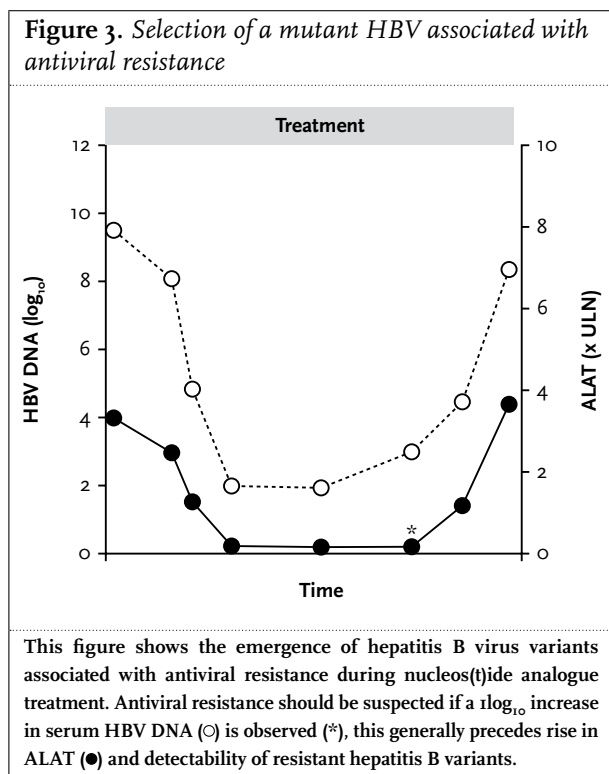
VIRAL SUPPRESSION OR IMMUNE MODULATION?

The approach to treatment of hepatitis B has rapidly changed over the past decade. The treatment landscape has advanced with the availability of multiple new antiviral agents. However, despite this major progress, long-term off-treatment control has not been achieved in a large proportion of patients. Worldwide, evidence-based treatment guidelines for the management of chronic hepatitis B have been developed.^{3,22,115} These documents make few specific recommendations as to whether pegylated interferon or nucleoside analogues should be used as first-line therapy. Because both approaches have proven effective, but also have advantages and limitations, the question arises what treatment regime should be used as first-line therapy. The major difference between these treatment strategies is providing sustained off-treatment response with a finite treatment course (IFN) vs therapy-maintained response (nucleoside analogues).

Of currently available antiviral agents, peginterferon-based therapies result in the highest probability of sustained off-treatment response. On the other hand, treatment with nucleoside analogues over prolonged periods is feasible and viral and biochemical response can generally be maintained. Since response to these agents is generally not durable after discontinuation of therapy, it is currently proposed that nucleoside analogue therapy needs to be continued indefinitely. This subsequently imposes a considerable risk for antiviral resistance. In our opinion, these findings provide a strong argument in favour of immunomodulatory therapy as first-line treatment for chronic hepatitis B.

Irrespective of the type of antiviral therapy used, sustained virological response results in improved biochemical, histological and clinical outcome. The main goal of antiviral therapy in chronic hepatitis B therefore remains achieving sustained viral suppression, preferably with a finite course of therapy. Individual patient characteristics such as age, comorbid disorders and likelihood to tolerate potential side effects should also be included in deciding on the optimal treatment regime.

Since PEG-IFN results in the highest rates of off-treatment response, treatment with this drug should be considered as first-line therapy in eligible patients with a high likelihood of response. This includes HBeAg-positive patients with genotype A or B, serum ALAT more than twice the upper limit of normal



and moderate HBV DNA levels (10^5 to 10^8 c/ml). Although data on PEG-IFN in HBeAg-negative chronic HBV are limited, PEG-IFN therapy may also be preferential in these patients. For patients with a low likelihood of response to or not eligible for PEG-IFN therapy, patients not tolerating PEG-IFN therapy, or with persistent hepatic inflammation and high viral load after a one-year course of PEG-IFN, treatment with nucleoside analogues should be considered. For several patient groups nucleoside analogues are the antiviral drug of choice. This includes patients with advanced cirrhosis, patients starting chemotherapy,¹¹⁶ immunocompromised patients,¹¹⁷ and pregnant patients with very high HBV DNA levels ($>10^9$ c/ml).¹¹⁸

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