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Concise Review

Current therapies for chronic hepatitis B

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Introduction

Chronic hepatitis B is a major public health problem and there are an estimated 400 million people worldwide infected with the Hepatitis B virus (HBV). It is one of the most common causes of hepatic cirrhosis and hepatocarcinoma.[1,2] The prevalence of chronic hepatitis B varies in different geographic locations. In the Western countries, hepatitis B is the third most common cause of chronic liver disease after hepatitis C and alcohol.

The principle objective of treatment is to control the replication of HBV and induce the remission of hepatic disease in order to stop progression to cirrhosis and hepatic cancer.[3,4] Treatment is indicated for patients with active inflammation, elevated aminotranferace (ALT) levels, and viral replication (HBV-DNA positive). It is agreed that patients with levels of HBV-DNA higher than 100,000 copies/mL should be treated.[3] Currently, there are three drugs approved for the treatment of chronic hepatitis B, the alfa interferons, lamivudine and adefovir dipivoxil.[3-6] Response to treatment is defined by normalization of ALT levels, DNA negativity or levels less than 100,000 copies/mL, the loss of HBeAg and seroconversion to anti-HBe. This response must occur during treatment and continue at least 6 to 12 months after the end of treatment.[5]

Interferons

For many years interferons have been the only treatment available for chronic hepatitis B. They have a notable immunomodulatory and anti-viral effect. Meta-analyses of interferons in patients with HBeAg positive chronic hepatitis have shown their efficacy. HBeAg negativity is induced in 30% of patients, while spontaneous negativity occurs in 10% of cases.[3] HBsAg loss occurs in 5% of cases in the first year and this increases to 11-20% after 5 years. Follow-up studies in responder patients demonstrate that this response is stable and persistent. In HBeAg positive chronic hepatitis, interferons are administered subcutaneously in doses from 5 million units daily to 10 million units 3 times per week for 16 to 24 weeks *(Table I)*. In anti-HBe positive patients with viral replication, interferons have a good response during treatment but the maintained response once treatment has ended is lower, between 10 and 40%. Furthermore, the recommended duration of treatment is at least 12 months at a dose of between 6 and 9 million units three times per week *(Table II)*.

The main drawbacks of the interferons are subcutaneous administration and their adverse events, which are frequent and which sometimes limit their use in treatment. The highest response to treatment is observed in patients with elevated ALT levels and low concentrations of HBV-DNA. Patients with advanced hepatic cirrhosis or decompensated liver disease respond badly to treatment and in many cases treatment is contra-indicated. HBV mutations have not been described in relation to treatment. Currently, studies are being performed with pegelated interferon, which has a longer half-life and permits once weekly administration. Preliminary results show a higher efficacy than standard interferon.

Table I. Approved drugs for the treatment of HBeAg positive hepatitis

- Interferons
  5-10 million units daily or 3 times per week subcutaneously for 16-24 weeks
- Lamivudine
  100 mg daily orally for at least 1 year. Recommended until seroconversion is achieved.
- Adefovir
  10 mg daily orally for at least 1 year . Recommended until seroconversion is achieved.

Table II. Approved drugs for the treatment of HBeAg negative hepatitis

- Interferons
  6-9 million units daily or thrice a week subcutaneously for at least 1 year.
- Lamivudine
  100 mg daily orally for at least 1 year. Indefinately??
- Adefovir
  10 mg daily orally for at least 1 year. Indefinately??

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Lamivudine

Lamivudine was the first orally administered antiviral drug approved for the treatment of chronic hepatitis B. Lamivudine is a nucleoside analogue, (-) enantiomer-2', 3'-didoxy-3'-thiacitidine, and it has a potent antiviral activity against the hepatitis B virus *in vitro* as *in vivo*.[8,9] The fundamental mechanism of action consists of inhibiting the synthesis of viral DNA. This inhibition is caused by the incorporation of lamivudine monophosphate into recently synthesized HBV-DNA, which interrupts that synthesis.[8,9] Lamivudine does not directly inhibit the production of viral proteins but its suppressive action is a consequence of the inhibition of the synthesis of viral DNA and the reduction in the functioning pools of covalently closed circular DNA (ccc-DNA). Due to this mechanism, the reduction of HBeAg and HBsAg in serum occurs more slowly than the reduction in viremia.[9,10]

Randomized studies with lamivudine (100 mg/day) for one year included more than 700 patients from Europe, Asia and the United States. These studies in patients with HBeAg positive chronic hepatitis B demonstrated that lamivudine could achieve seroconversion to anti-HBe in 16 to 18% of treated patients compared with 4 to 6% in controls.[7-10] The virologic response was associated with an improvement in necro-inflammatory activity and hepatic fibrosis, a reduction in the progression to cirrhosis, and the normalization of ALT levels.[11-12] Lamivudine is also efficacious in patients previously unresponsive to interferon, the response to lamivudine being the same as in previously untreated patients (18% seroconversion to anti-HBe with lamivudine).[10]

The accumulative rate of seroconversion to anti-HBe was higher in patients with elevated ALT levels,[11] and it increases progressively with longer lamivudine treatment.[12,13] Studies performed with Chinese patients treated with lamivudine for more than 3 years have demonstrated that the accumulative rate of seroconversion increases from 22% after one year of treatment to 40% when treatment is prolonged to 3 years.[13] Also, in some patients, the appearance of anti-HBe antibodies is followed by the loss of HBsAg and seroconversion to anti-HBs.

The safety profile of lamivudine is excellent, similar to placebo and this permits its use in patients with advanced hepatic illness and decompensated cirrhosis. The response in hepatitis B patients with precore mutations (anti-HBe positive) is similar to patients infected by the wild type. Sixty five percent of patients treated with lamivudine for one year presented negative HBV-DNA and normal ALT levels.[14] However, after the end of treatment, this was maintained in only 12-14% of cases.[15]

Lamivudine and HBV variants

In some patients, during treatment with lamivudine, distinct variants in the nucleotide sequence of the HBV genome have been identified.[16-18] These variants are seen in both immunocompetent and immunosuppressed patients, although they are more frequent in the latter, i.e. liver transplanted patients and those infected by the human immunodeficiency virus (HIV). These variants are produced in the P gene, which codifies the HBV polymerase, and commonly in the YMDD motif of this region. Three types of changes have been observed in and around the YMDD region (amino acid sequence tirosine-methionine-aspartate-aspartate).[16-18] This region forms part of the site where HBV polymerase DNA nucleotides connect. The variants most commonly detected consist of a substitution of a methionine by a valine (M552V or M550V) or an isoleucine (M552I or M550I) in this segment. Other variants in amino acids before the YMDD region have also been detected, such as the substitution of a isoleucine for a methionine (L528M or L526M) which are associated with variants M552V and M552I.

Kinetic enzyme analysis suggests that these changes alter the interactions between the lamivudine triphosphate and the HBV polymerase, although the polymerase continues functioning.[18] Therefore, the variants in the YMDD region (YVDD, YIDD) can continue replicating, despite the presence of lamivudine. In the end, the pressure imposed by the lamivudine determines that the mutated variants in the YMDD region become the dominant HBV strain.[19,20]

YMDD variants do not multiply as efficaciously as the wild type *in vitro*.[19,20] This phenomenon has been verified by molecular cloning technique. The altered DNA (with mutations in the YMDD region) is transferred to tissue culture cells and the rate of viral production measured. Mutations in the YMDD region can be seen to present a certain resistance to lamivudine in vitro. However, this analysis also reveals that YMDD strains have a lower capacity for replication than wild type HBV, no doubt because the viral polymerase has less affinity with the substrates (nucleotides). There are also clinical information and experimental models demonstrating that wild type HBV reemerges as the dominant strain once treatment has ended and the selective pressure of lamivudine has disappeared.[18] However, in some cases, variants in the YMDD region persist for a prolonged period of time after treatment is discontinued.

HBV strains with lamivudine resistant mutations in theYMDD region are usually first detected in the first 6 to 9 months of treatment. At one year of treatment, these variants appear in 14 to 32% of patients and this increases with longer treatment to 42% and 52% of patients at 2 and 3 years respectively.[19,20] The emergence of these strains is accompanied by an increase in ALT levels and

the reappearance of HBV-DNA and their appearance is directly related to baseline serum concentrations of HBV-DNA, ALT levels and high body mass index. When lamivudine treatment ends or is interrupted, the percentage of patients with variants in the YMDD region is considerably lower in the following months.

Clinical significance of mutations in the YMDD region in patients with chronic hepatitis B treated with lamivudine

The majority of patients with mutations in the YMDD region are asymptomatic. However, the behaviour of these mutations over the long term is still unknown. Occasionally, complications in the form of decompensated hepatic disease occur, most often in patients who have already had an advanced liver disease. However, preliminary results in Asian patients treated with lamivudine for more than 3 years show that patients with variants in the YMDD region have higher probabilities of presenting deterioration in liver histology than those without YMDD mutations.

The appearance of mutations in the YMDD region is associated with increases in ALT levels, and the reappearance of circulating HBV-DNA, usually at levels lower than baseline and this is associated with a reduction in the HBeAg seroconvesion rate. After 3 years of lamivudine treatment, seroconversion to anti-HBe is seen in 22% of patients with variant strains in the YMDD region, compared with 50% in patients without these strains. Lamivudine is especially useful in patients with terminal hepatic disease and liver transplant candidates. Various studies demonstrate that the rate of HBV-DNA negativization is similar to that observed in patients with compensated chronic hepatitis.[21-23] HBV-DNA clearance is associated with an improvement in hepatic illness, permitting in some cases, the delay or even avoidance of liver transplant. In patients with advanced hepatic disease, the emergence of mutations in the YMDD region can be accompanied by a deterioration of the disease due to ictericia, ascitis and other complications associated with portal hypertension. In some transplantation centres, HBV-DNA positivity is a contra-indication for transplant since it is associated with a higher risk of HBV reinfection. The recurrence rate of HBV reinfection is higher in patients who had serum HBV-DNA and mutations in the YMDD region before liver transplantation. In these cases, HBV reinfection occurs earlier and despite specific prophylaxis with gammaglobulin and lamivudine and for this reason it is important to identify patients with YMDD mutations in order to select the most appropriate treatment.[24,25] It is very important to identify the different variations, since in vitro studies have shown that resistance to lamivudine is varies depending on the mutated amino acid and its position. Variations in amino acid 552 (changing to valine and/or isoleucine) and the double variation at position 528 and 552 offer the most resistance to the drug. However, both variations are sensitive to treatment with adefovir.[26]

Adefovir dipivoxil

Adefovir dipivoxil, the prodrug of adefovir, is an orally administered nucleotide analogue. It inhibits the HBV-DNA polymerase (reverse transcriptase) by competing with the natural substrate and by causing DNA chain termination after its incorporation into viral DNA. Adefovir has been approved for the treatment of chronic hepatitis B. The largest study in HBeAg positive patients demonstrated that the administration of 10 mg of adefovir for one year is capable of reducing the histological hepatic activity index (> 2 points in 53% of cases compared with 25% in cases on placebo). The loss of HBeAg is seen in 24% of cases and seroconversion to anti-HBe in 12% compared to 6% in subjects who received placebo.[27] There are still no published studies of prolonged treatment although some abstracts presented at conferences suggest an increase in response to prolonged treatment.

There is one study in anti-HBe positive patients treated with adefovir for one year and compared with a control group.[28] The study included 184 patients who were randomised to receive adefovir or placebo. An analysis of the results demonstrated that a histological response was observed in 64% of treated patients *vs.* 33% in controls, normalization of ALT levels occurred in 72% of those treated *vs* 29% in controls and HBV-DNA negativity by PCR in 51% *vs.* 0% respectively.

Adefovir is especially useful in patients with resistance to lamivudine.[29-33] Studies *in vitro* and *in vivo* have demonstrated that adefovir is able to inhibit wild type HBV strains and those resistant to lamivudine. In more than 100 patients with decompensated cirrhosis and resistance to lamivudine, treatment with 10 mg of adefovir produced a more than 4 log reduction in concentrations of HBV-DNA during 24 weeks of treatment. This reduction in HBV-DNA levels was accompanied by a decrease in ALT levels and an improvement in Child-Pugh scores. Similar results have been observed in liver transplanted patients with recurrent HBV infection. Adefovir continued to inhibit HBV replication with reductions of 3-4 logs in HBV-DNA during 48 weeks of treatment.

Finally, there is one ongoing study comparing the combination of adefovir *vs.* lamivudine and adefovir or adefovir monotherapy in patients with resistance to lamivudine. Preliminary results demonstrate that monotherapy with adefovir achieves the same reduction in HBV-DNA levels as combined treatment with adefovir and lamivudine, suggesting that the use of adefovir is sufficient in patients with lamivudine resistance.[39]

The recommended adefovir dose is 10 mg daily and the dose has to be adjusted for patients with renal insufficiency. The optimum duration of treatment has not been defined but is probably more than one year. However, experience with this drug is still limited especially with therapy prolonged to more than two years. The durability of response once therapy has finished is similarly not well documented. The most serious adverse event is the alteration of renal function when using doses larger than 10 mg, however, the long term safety of this drug has not been established. In studies of adefovir for one year, resistance to the drug has not been observed, which, if confirmed in longer term studies, would be an advantage of adefovir, although it is probably over the long term that resistance would appear.

In conclusion, the future of hepatitis B therapy is promising. In addiction to the drugs already approved, there are others currently in phase 3 of clinical trials such as Entecavir, the L nucleosides and emtricitabine, which shows a powerful specific activity against the hepatitis B virus. If these drugs demonstrate their efficacy and safety, HBV therapy is going to expand and a new era is going to start using these new drugs and particularly combination therapy.

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