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Hepatitis B e Antigen Seroconversion: Effects of Lamivudine Alone or in Combination With Interferon Alpha

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Seroconversion of hepatitis B e antigen (HBeAg) is an important marker for resolution of active hepatitis B virus (HBV) infection and for a long-term positive response to treatment. Lamivudine, a nucleoside analogue, is the first effective oral treatment for chronic hepatitis B in patients with evidence of viral replication and liver disease. When appropriate patient groups are compared, treatment with lamivudine for 1 year leads to HBeAg seroconversion in a similar proportion of patients as a standard course of interferon (IFN) alpha therapy. Seroconversion increases during prolonged therapy (up to 3 years), and is sustained post-treatment in more than three-quarters of patients. Response rates are related to the pretreatment level of serum alanine aminotransferase (ALT) and reach 65% in those patients with serum ALT > 5 × upper limit of normal (ULN) after one year. For patients with pretreatment ALT > 2 × ULN, response was seen in 38% after one year, rising to 65% after 3 years. To date, combination with IFN and lamivudine has not been shown to confer additional benefit compared with lamivudine monotherapy. Lamivudine is effective and appropriate for use in a greater proportion of HBV infected patients than IFN alpha, particularly those infected at birth or in early childhood. Furthermore, because seroconversion after lamivudine is not normally associated with a severe flare of liver disease, as seen with IFN, it is more suitable for use in patients with active liver disease and cirrhosis. In conclusion, lamivudine is more suitable than IFN for a broad range of patients, including those with severe liver disease, recurrent flares, pre-core mutant HBV and those who have failed previously IFN treatment or are immunosuppressed. Lamivudine is also better tolerated than IFN. ***J. Med. Virol. 61:374–379, 2000.***

KEY WORDS: chronic hepatitis B; pathogenesis; hepatitis B e antigen seroconversion

INTRODUCTION

Hepatitis B e antigen (HBeAg) seroconversion is loss of detectable HBeAg together with detection of antibodies to HBeAg (anti-HBe); ideally it includes loss of detectable serum HBV DNA by solution hybridisation assays but this has not always been carried out in earlier studies. Some patients with durable HBeAg loss do not gain anti-HBe [Alexander et al., 1987; Catterall et al., 1993], and therefore cannot be considered as having seroconverted using this definition.

HBeAg seroconversion signals a watershed in the natural history of chronic hepatitis B. In particular, it is associated with a substantial reduction in the risk of liver failure, even if cirrhosis has developed during a prolonged immuno-elimination phase. Seroconversion is therefore a key endpoint in studies investigating the efficacy of different agents for treatment of chronic hepatitis B.

PATHOGENESIS OF CHRONIC HEPATITIS B

The pathogenesis of chronic hepatitis B [Dusheiko, 1999] involves both the HBV infection and the T-cell mediated immune response to the viral epitopes that are expressed on the surface of infected hepatocytes. After acquisition of infection at birth or in early childhood, the infection typically passes through three stages: the high replicative immune tolerance phase, the low replicative immune clearance phase and the non-replicative residual integrated phase [Chu et al., 1985; Chu and Liaw, 1997].

Immune Tolerance Phase

Initially, patients' immune systems are very tolerant of the virus. Reflecting this, there are usually high levels of virus replication, as indicated by high serum titres of HBeAg and HBV DNA, with effectively no or minimal demonstrable T-cell immune response and consequently no signs or symptoms of liver disease. Immune tolerance is an active process (it requires T-

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cell suppression) and this phase may last from a few weeks to more than 10 years [Chu and Liaw, 1997].

Immune Clearance Phase

Some time later, often toward the late teen years or in the third and fourth decades of life, the immune tolerance to the virus wanes. This is associated with decreased serum titres of HBeAg and HBV DNA, increased serum alanine aminotransferase (ALT) concentrations and active inflammatory activity in the liver, indicative of attempts by the immune response to eliminate HBV-infected hepatocytes. Clearance of infected hepatocytes often results in a flare of liver disease and elevated serum ALT, subsequently followed by normalisation of serum ALT levels. In most adult patients who are infected as a result of their occupation or lifestyle, this is a successful process that probably takes place over a relatively brief period of time, possibly only a few weeks or months. The clearance phase normally passes unnoticed and leads to a state of non-replicative infection. Some residual HBV supercoiled DNA remains, as do some of the integrated viral genomes, but there is no active free or episomal virus replication. HBV core constituents (hepatitis B core antigen [HBcAg], HBeAg and HBV DNA) are no longer expressed on hepatocytes or released into the serum, resulting in serum HBeAg negativity, the appearance of anti-HBe and undetectable HBV DNA using hybridisation assays. Seroconversion is usually associated with permanent suppression of HBV replication and loss of indicators of virus replication [Chu and Liaw, 1997]. Clinically, it is associated with normalisation of ALT, a reduction in necro-inflammatory activity or hepatitis in the liver, the arrest of fibrosis and fibrotic progression and, in those patients who have relatively severe disease, it is also associated with functional improvement. These changes also reduce the risk of clinical complications such as liver failure, liver-related death and, consequently, the need for transplantation [Niederau et al., 1996; Liu et al., 1999].

Chronic hepatitis B follows a failure of the usual elimination phase, that results from ineffective clearance of HBV with continued destruction of the infected hepatocytes. At the clinical level, this is associated with elevation in serum ALT levels, and it is this abnormally protracted phase that is the target for antiviral or immunomodulatory treatment.

Residual Integrated Phase

In this phase there is the continued presence of hepatitis B surface antigen (HBsAg) without virological, serological or histological evidence of HBV replication and hepatitis [Chu and Liaw, 1997].

Clinical Relevance of HBeAg Seroconversion

The importance of HBeAg seroconversion in the natural history and the clinical outcomes of chronic hepatitis B is well illustrated by the improvement in clinical outcome after spontaneous or interferon (IFN) alpha-induced HBeAg seroconversion. One cohort of European patients was followed for a 5-year period until the occurrence of a major liver-related complication, such as ascites, variceal bleeding, liver transplant, liver-related death or hepatocellular carcinoma. None of the patients who responded to IFN alpha had any major liver-related complication. In contrast, those patients who failed to lose HBeAg, whether treated with IFN alpha or untreated, had more clinical complications, with approximately 50% of patients surviving after 5 years [Niederau et al., 1996].

IFN AND HBeAg SEROCONVERSION

Until recently, the only licensed form of therapy for HBV infection has been IFN alpha. IFN alpha acts principally as an immunomodulatory agent. It is most effective when the immune system is sufficiently primed to achieve an immune elimination through augmentation of the existing response. Clinically, a high serum ALT concentration is the best correlate of the primed and reactive state. Consequently, the best indicators for IFN alpha effectiveness are a very high ALT, a low HBV DNA, and a short duration since the onset of HBV [Perrillo, 1994]. In this highly selected patient population, that is not typical of infection in those countries with the greatest burden of HBV disease, IFN alpha is an effective therapeutic option. In practice, this translates into good response rates (up to 40%) if ALT concentrations are more than 3-fold above the upper limit of the normal reference range (3 × ULN), and a lower response rate (5–15%) in the more common situation of lower pre-treatment serum ALT levels. Some patients achieving HBeAg seroconversion also eventually lose hepatitis B surface antigen (HBsAg), that may lower further the risk of liver cancer or liver-related death [Korenman et al., 1991; Perrillo, 1993; Fattovich et al., 1998].

The principal problem associated with IFN alpha treatment is that it is unsuitable for the vast majority of patients with chronic hepatitis B because they tend to have poor immune responsiveness, low ALT levels and prolonged infection as a result of childhood onset. In addition, the pre-core mutant type of HBV, that is predominant in many countries, does not respond well to IFN alpha [Hadziyannis et al., 1990; Pastore et al., 1992; Brunetto et al., 1993]. Further, the HBeAg seroconversion induced by IFN alpha is often preceded by an abrupt, transient accentuation of hepatitis activity, as reflected by an increase in serum ALT in patients with severe liver disease [Marinos et al., 1994; Perrillo, 1994; Gaeta et al., 1995; Hassanein et al., 1996]. In patients with cirrhosis, this flare of activity can lead to liver failure and occasional deaths. Because of these limitations, IFN alpha treatment is useful for only 2–5% of patients with chronic hepatitis B in Asian–Pacific countries, and is contraindicated in patients with advanced cirrhosis in whom treatment is most necessary. Finally, IFN alpha is not particularly easy to use (being inconvenient to administer), has many undesir-

able adverse effects, and is expensive [Wong et al., 1993; Hoofnagle and Di Bisceglie, 1997; Schiff, in press].

LAMIVUDINE AND HBeAg SEROCONVERSION

Lamivudine is an inhibitor of the HBV RNA-dependent DNA polymerase and is therefore a potent suppressor of HBV replication. Within 4 weeks, a course of lamivudine therapy suppresses serum HBV DNA to undetectable levels in 90% of cases, as determined by most commercial assays [Tyrrell et al., 1993; Dienstag et al., 1995; Nevens et al., 1997; Lai et al., 1997]. Although such an agent might not be expected to influence immune responsiveness directly, *in vitro* studies have shown that the reduction in the circulating levels of viral proteins induced by lamivudine may promote indirectly a more vigorous immune response [Boni et al., 1998]. In addition, lamivudine has high oral bioavailability, with a pharmacokinetic profile that makes it suitable for single daily dosing [Johnson et al., 1999]. It is well tolerated, so that even minor adverse effects are unusual [Leung et al., 1998]. After 12 months of continuous lamivudine therapy, about two-thirds of patients will have a normal ALT, and most will not have detectable serum HBV DNA [Lai et al., 1998]. Furthermore, lamivudine therapy arrests progression of hepatic fibrosis, it may allow fibrotic regression and it reduces progression to cirrhosis [Lai et al., 1998; Goodman et al., 1999; Leung, in press]. There is no doubt, therefore, that lamivudine interrupts the natural history of chronic hepatitis B with virus suppression. Lamivudine also reduces viral load, normalises serum ALT and improves liver histology during treatment of chronic hepatitis B associated with precore mutants [Tassopoulos et al., 1999; Rizzetto, in press].

Now that lamivudine is available for the treatment of chronic hepatitis B, it is important to establish when it is possible to discontinue therapy. Seroconversion does occur after 12 months of lamivudine treatment; the rates achieved in several Phase III trials are shown in Figure 1 [Lai et al., 1998; Schiff et al., 1998a; Dienstag et al., 1999a; Schalm et al., 2000]. The proportion of patients achieving HBeAg seroconversion after 12 months of lamivudine treatment (100 mg daily) has ranged consistently between 16 and 18%, compared with 4–6% in the placebo groups in most studies [Dienstag et al., 1999a; Lai et al., 1998]. Thus, HBeAg seroconversion can be achieved after only 12 months of therapy in about three to four times more patients than would be expected to occur spontaneously. IFN alpha resistant patients respond to lamivudine just as well as those who have not been previously treated [Schiff et al., 1998a].

Exploratory analyses of data for patients enrolled in one of these studies [Lai et al., 1998] showed that the pre-treatment serum ALT concentration was the most important determinant of HBeAg seroconversion [Chien et al., 1999]. The likelihood of seroconversion

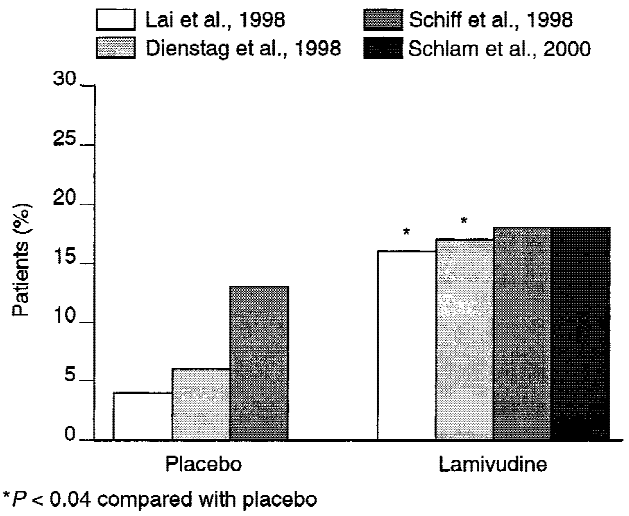

Fig. 1. Lamivudine leads to hepatitis B e antigen (HBeAg) seroconversion (HBeAg-negative, anti-HBe-positive, HBV DNA-negative) tested by a hybridisation assay. Data from Dienstag et al. [1999a]; Schalm et al. [2000]; Lai et al. [1998]; Schiff et al. [1998a].

increased with increasing pre-treatment serum ALT levels and was highest in patients in whom pre-treatment serum ALT concentrations exceeded 5 × upper limit of normal (ULN) (65%) (Fig. 2).

The response to IFN alpha depends on pre-treatment HBV DNA concentrations. This is also true of lamivudine with respect to HBeAg seroconversion [Perrillo et al., 1999]. Patients with low serum HBV DNA concentrations are more likely to achieve seroconversion after 12 months of treatment than those with a high serum concentration of HBV DNA. One of the most interesting differences between lamivudine and IFN alpha therapy is that the proportion of patients achieving seroconversion with lamivudine seems to be the same in different ethnic groups. When the results of the Phase III studies in Caucasian populations in North America and Europe were compared with results in Asian patients, after controlling for pre-treatment serum ALT levels, HBeAg responses did not differ appreciably. After 1 year of therapy, 17% of Asians and 18% of Caucasians showed evidence of seroconversion. [Dienstag et al., 1999b]. Therefore, the only pre-treatment predictors of HBeAg seroconversion during lamivudine therapy that need be considered are serum ALT and HBV DNA. Unlike IFN alpha therapy, other demographic and disease-related factors, such as age, sex, ethnicity, mode of acquisition, previous IFN therapy, fibrotic stage of liver disease or the presence of cirrhosis, have no influence on the outcome of lamivudine therapy [Gitlin, 1997; Lai et al., 1998; Schiff et al., 1998b; Dienstag et al., 1999b; Yao et al., 1999]. Follow-up studies [Korenman et al., 1991] of IFN alpha therapy show that HBeAg seroconversion is maintained post-therapy in most individuals (80–90%). Similar sustained response rates are observed after lamivudine treatment [Schiff et al., 1998b].

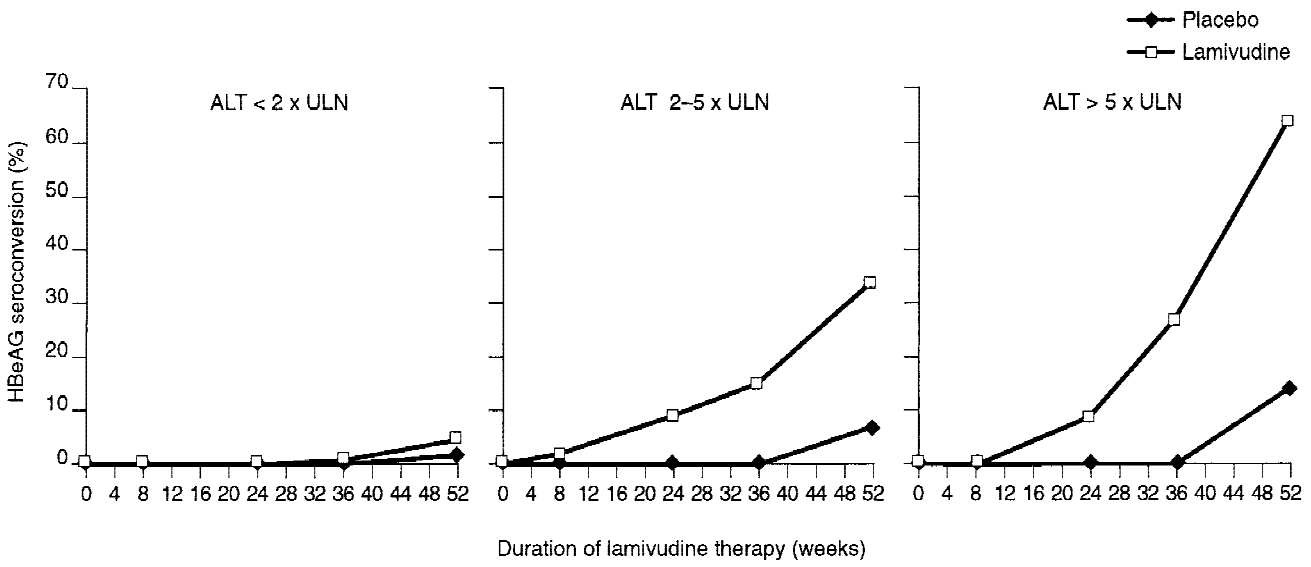

Fig. 2. The relationship between seroconversion during lamivudine therapy and baseline serum alanine aminotransferase (ALT) level. HBeAg, hepatitis B e antigen (HBeAg); ULN, upper limit of normal. Data from Chien et al. [1999].

SEROCONVERSION DURING PROLONGED TREATMENT WITH LAMIVUDINE

A subgroup of 58 patients from the Asian Phase III study [Lai et al., 1998] have been treated with lamivudine continuously for 3 years. The proportion of patients who lost HBeAg and gained anti-HBe increased from 22% (13/58) after treatment for 1 year, to 40% (23/58) after treatment for 3 years [Chang et al., 1999]. These findings are from the patient group as a whole, i.e., including patients with elevated pre-treatment serum ALT levels as well as patients with normal pretreatment ALT levels, who would not be expected to respond as readily to treatment. When only those patients with a pretreatment serum ALT levels greater than 2 × ULN were considered, the proportion of patients with loss of HBeAg and gain of anti-HBe after 3 years increased to 65% (17/26) [Chang et al., 1999]. These early results indicate that extended duration of lamivudine therapy is likely to lead to more patients undergoing seroconversion.

IFN ALPHA AND LAMIVUDINE COMPARED AND COMBINED

Attempts have been made to compare directly the efficacy of IFN alpha and lamivudine and a combination of the two drugs in patients with chronic hepatitis B. However, such studies are difficult to design because of the different routes of administration and the different durations of treatment. In a preliminary study of IFN alpha non-responders treated for 12–16 weeks with combination therapy, four (20%) patients showed HBeAg seroconversion, but this was sustained in only a single patient [Mutimer et al., 1998]. In a larger study of IFN alpha non-responders, 18% of patients treated with lamivudine monotherapy for 52 weeks achieved seroconversion compared with 12% of those treated with combination therapy [Schiff et al., 1998a]. Schalm et al. [2000] compared lamivudine alone for 52 weeks, IFN alone for 16 weeks and the combination in previously untreated patients. Although the proportion of patients achieving HBeAg seroconversion was higher in the combination treatment group than in either monotherapy group (29% vs. 19% of lamivudine-treated patients and 18% of IFN alpha-treated patients), this did not achieve statistical significance. Interestingly, there seemed to be no advantage for those patients with high pre-treatment ALT concentrations; instead, it was those patients with intermediate serum ALT concentrations who seemed to do better with combination treatment. The adverse effects of combination therapy were the same as those observed with IFN alpha alone. It remains possible that future studies may identify a subgroup of patients that might benefit from combining lamivudine with immunomodulatory agents, but this requires further investigation.

CONCLUSIONS

Treatment with lamivudine results in rapid and profound suppression of HBV replication, followed by HBeAg seroconversion in a high proportion of patients with raised pretreatment serum ALT. Moreover, HBeAg seroconversion that occurs during lamivudine treatment is generally sustained post-treatment. Such a sustained response seems to be obtained at least as often with lamivudine as with IFN alpha for comparable groups, especially with respect to the pretreatment ALT level, and combination of IFN alpha with lamivudine does not seem to confer major benefit.

Lamivudine is more suitable than IFN alpha for a broad range of patients, including those with severe liver disease, recurrent flares, pre-core mutant HBV-

related disease and those who have previously failed IFN alpha treatment or are immunosuppressed, and it has limited side-effects and great patient acceptability.

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