

The effects of lamivudine and recombinant hepatitis B vaccine on chronic carriers of hepatitis B

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ABSTRACT

The purpose of this study was to determine the effects of lamivudine and recombinant hepatitis B vaccine on chronic hepatitis B carriers. Studies has been shown that in animal models chronic Hepatitis B Vaccination can enhance immune response. Furthermore, treatment with lamivudine has resulting contributes to the maintenance of cellular immune responses than hepatitis antigen B. In this study, a group of eligible patients were divided into three groups. Lamivudine therapy and Vaccination were done in groups 1. In groups 2 lamivudine were used alone. In addition, The third group were used as control. The Fisher exact test was used for data analysis and differences among treatment in this study. The results showed that the only significant difference in the HBs Ag sreoconversion rates were observed between groups 1and control groups at the end of the fifteenth month. The present investigation suggested that the adjuvant therapy with hepatitis B vaccine together with lamivudine in chronic carriers of hepatitis B may lead to the eradication of viral infection in these patients.

Key words: HBs Ag sreoconversion, Recombinant hepatitis B vaccine, Chronic carriers of hepatitis B

INTRODUCTION

Hepatitis B is an infectious inflammatory illness of the liver caused by the hepatitis B virus (HBV) that affects hominoidea, including humans. Originally known as "serum hepatitis", the disease has caused epidemics in parts of Asia and Africa, and it is endemic in China. About a third of the world population has been infected at one point in their lives, including 350 million who are chronic carriers. The virus is transmitted by exposure to infectious blood or body fluids such as semen and vaginal fluids, while viral DNA has been detected in the saliva, tears, and urine of chronic carriers. Perinatal infection is a major route of infection in endemic (mainly developing) countries [5]. Other risk factors for developing HBV infection include working in a healthcare setting, transfusions, dialysis, acupuncture, tattooing, sharing razors or toothbrushes with an infected person, travel in countries where it is endemic, and residence in an institution. However, hepatitis B viruses cannot be spread by holding hands, sharing eating utensils or drinking glasses, kissing, hugging, coughing, sneezing, or breastfeeding. Acute infection with hepatitis B virus is associated with acute viral hepatitis—an illness that begins with general ill-health, loss of appetite, nausea, vomiting, body aches, mild fever, and dark urine, and then progresses to development of jaundice. It has

been noted that itchy skin has been an indication as a possible symptom of all hepatitis virus types. The illness lasts for a few weeks and then gradually improves in most affected people. A few people may have more severe liver disease (fulminant hepatic failure), and may die as a result. The infection may be entirely asymptomatic and may go unrecognized. Chronic infection with hepatitis B virus either may be asymptomatic or may be associated with a chronic inflammation of the liver (chronic hepatitis), leading to cirrhosis over a period of several years. This type of infection dramatically increases the incidence of hepatocellular carcinoma (liver cancer). Chronic carriers are encouraged to avoid consuming alcohol as it increases their risk for cirrhosis and liver cancer. Hepatitis B virus has been linked to the development of Membranous glomerulonephritis (MGN). Immunosuppression due to the underlying disease or to drugs used in autoimmune diseases, anticancer therapy and in organ transplants can influence the hepatitis B virus (HBV), both in terms of reactivation and in terms of the acceleration of a pre-existing chronic hepatitis. In this situation, the possibility of HBV relapse has been known for years, with clinical manifestations ranging from self-limiting anicteric to fulminant forms or to chronic hepatitis with an accelerated clinical course towards liver decompensation. In most cases, hepatitis B develops at the time of immune reconstitution as a consequence of the antiviral immune response and less frequently at the time of the enhanced replication during massive immunosuppression. Moreover hepatitis reactivation may influence the continuation of the specific treatments and the survival of immunosuppressed or transplanted patients [17]. The risk of clinical events is mainly observed in overt carriers of HBV, but can also develop in the "occult" condition of infection which has been widely described in the literature of the last decade [15]. Progress in the diagnostic procedures of the various virological conditions associated with HBV and in particular the recent availability of effective antiviral treatments has brought this problem to the fore although it is still debated. Hepatitis B virus (HBV) infection is a serious global health concern. Approximately 350 million people worldwide are chronically infected, and 500,000 to 1.2 million deaths per year are attributed to HBV-associated complications [12]. A common variant of HBV infection occurs in patients who test negative for hepatitis B e antigen (HBeAg) and positive for antibodies against HBeAg (anti-HBe) and in whom serum HBV DNA and alanine aminotransferase levels remain persistently or intermittently elevated [10, 8]. The median worldwide prevalence of HBeAg-negative disease in hepatitis B surface antigen (HBsAg)-positive carriers was reported to be 33 percent in 2002 and is increasing [8]. HBeAg-negative HBV develops spontaneously through mutations in the precore or core promoter regions of the viral genome such that HBeAg is no longer expressed or is down regulated, and it has been suggested that this gives the mutant an immunologic advantage over wild-type HBV [10, 9]. However, HBeAg-negative chronic hepatitis B is a heterogeneous condition, and wild-type HBV may also be responsible for disease activity in some patients [2, 18]. The clinical profile of HBeAg-negative chronic hepatitis B differs from that of HBeAg-positive disease in that patients are typically older, serum HBV DNA levels are usually lower, and liver disease tends to fluctuate [7, 16]. Patients with HBeAg-negative chronic hepatitis B have more advanced liver disease, and the likelihood of spontaneous remission is very low [9, 3]. The end point of treatment for HBeAg-negative chronic hepatitis B is unknown. HBeAg loss or seroconversion cannot be used to assess response, and treatment usually focuses on suppression of HBV DNA and normalization of alanine aminotransferase levels [6]. Effective suppression of HBV DNA without development of resistance among HBeAg-negative patients has been associated with improved histologic findings in the liver and long-term clinical benefit [13]. Treatment guidelines support the use of interferon, lamivudine, or adefovir for HBeAg-negative chronic hepatitis B in patients with viremia and elevated alanine aminotransferase levels. These guidelines have been written to assist physicians and other health care providers in the recognition, diagnosis, and management of patients chronically infected with the hepatitis B virus (HBV). They are intended to suggest preferable approaches to the clinical management of chronic hepatitis B. The recommendations are flexible and are not intended as the only acceptable approach to management and treatment. As the appropriate course of treatment will vary in light of the relevant facts and circumstances surrounding each individual patient with chronic hepatitis B, guidelines are not intended to define the applicable standard of medical care and may be updated periodically as new information becomes available. Symptoms outside of the liver are present in 1–10% of HBV-infected people and include serum-sickness-like syndrome, acute necrotizing vasculitis (polyarteritis nodosa), membranous glomerulonephritis, and papular acrodermatitis of childhood (Gianotti-Crosti syndrome). The serum-sickness-like syndrome occurs in the setting of acute hepatitis B, often preceding the onset of jaundice. The clinical features are fever, skin rash, and polyarteritis. The symptoms often subside shortly after the onset of jaundice, but can persist throughout the duration of acute hepatitis B. About 30–50% of people with acute necrotizing vasculitis (polyarteritis nodosa) are HBV carriers. HBV-associated nephropathy has been described in adults but is more common in children. Membranous glomerulonephritis is the most common form. Other immune-mediated hematological disorders, such as essential mixed cryoglobulinemia and aplastic anemia. The present study was conducted to evaluate the effects of lamivudine and recombinant hepatitis B vaccine on chronic carriers of hepatitis B.

MATERIALS AND METHODS

This study was conducted in the Loghman, Shahid Labbafi nejad hospital Clinic of Infectious and Pasteur Institute of Iran from 2003 to 2004 years. In this study, a group of eligible patients were divided into three groups. Lamivudine therapy and Vaccination were done in groups 1. In groups 2 lamivudine were used alone. In addition, the third group were used as control. In this experiment, 51 patients ranging in age from 18 to 40 years old were examined. Inclusion criteria for this study are HBs Ag ⁺, HBs Ag ⁻, IgM anti HBC ⁻, IgG anti HBC ⁺, normal liver enzymes and written consent of the patient. Because of lack of consent and cooperation, one patient from group 1, three patients of the second group and three patients in the control group were removed from this experiment. The Fisher exact test was used for data analysis and differences among treatment in this study.

RESULTS AND DISCUSSION

The age and sex distribution of patients in different groups of this experimental are presented in Table 1. The amount of HBs Ag sreoconversion in treatments at the end of the month twelfth and fifteenth are presented in Table 2. The amount of HBs Ag sreoconversion at the end of the month twelfth is 18/75 in group ₁, 7/14 in group ₂ and 0 in control group. The amount of HBs Ag sreoconversion at the end of the month fifteenth are 31/25, 7/14 and 0 respectively in group ₁, group ₂ and control group.

Table 1. The age and sex distribution of patients in different groups of this experimental

Variable	Group ₁	Group ₂	Control	P-Value
Number (n=)	16	14	14	
Age	31.42±8.51	30.63±9.24	29.75±11.2	NS
Gender (Male to female)	11/5	8/4	10/4	NS

*NS: Non Significant

Table 2. The amount of HBs Ag sreoconversion in treatments at the end of the month twelfth and fifteenth

HBs Ag sreoconversion	N	Twelfth month	Fifteenth month
Group ₁	16	3 (18.75)	5 (31.25)
Group ₂	14	1 (7.14)	1 (7.14)
Control	14	0	0

Hepatitis B vaccine is a vaccine developed for the prevention of hepatitis B virus infection. The vaccine contains one of the viral envelope proteins, hepatitis B surface antigen (HBsAg). It is produced by yeast cells, into which the genetic code for HBsAg has been inserted. A course of two to three (2-3) vaccine injections are given, the second injection at least one month after the first dose and the third injection being administered six months after the first dose. The first and second dose offer complete protection. The final injection (second or third depending on number of vaccines being administered) is to prolong protection against the hepatitis B virus. Afterward an immune system antibody to HBsAg is established in the bloodstream. The antibody is known as anti-HBsAg. This antibody and immune system memory then provide immunity to hepatitis B infection. The first vaccine became available in 1981. The invention of the vaccine began with the realization (by virologist Alfred Prince, in 1968) that the Australia antigen was part of a virus that caused hepatitis B. Maurice Hilleman at Merck used three treatments (pepsin, urea and formaldehyde) of blood serum together with rigorous filtration to yield a product that could be used as a safe vaccine. Hilleman hypothesized that he could make an HBV vaccine by injecting patients with hepatitis B surface protein. In theory, this would be very safe, as these excess surface proteins lacked infectious viral DNA. The immune system, recognizing the surface proteins as foreign, would manufacture specially shaped antibodies, custom-made to bind to, and destroy, these proteins. Then, in the future, if the patient were infected with hepatitis B virus, the immune system could promptly deploy protective antibodies, destroying the viruses before they could do any harm. Hilleman devised a multistep process to purify this blood so that only the hepatitis B surface proteins remained. Every known virus was killed by this process, and Hilleman was confident that the vaccine was safe. The first large-scale trials for the blood-derived vaccine were performed on gay men, considered to be an at-risk group. Later, Hilleman's vaccine was falsely blamed for igniting the AIDS epidemic. But, although the purified blood vaccine seemed questionable, it was determined to have indeed been free of HIV. The purification process had destroyed all viruses including HIV. The vaccine was approved in 1981. It was withdrawn from the marketplace when Pablo DT Valenzuela, Research Director of Chiron Corporation succeeded in 1986 in making the antigen in

yeast and invented the first recombinant vaccine. The recombinant vaccine was developed by inserting the HBV gene that codes for the surface protein into a species of yeast called *Saccharomyces cerevisiae*. This allows the yeast to produce only the noninfectious surface protein, without any danger of introducing actual viral DNA into the final product. Babies born to mothers who've had the hepatitis virus are vaccinated with hepatitis B surface antigen (HBsAg) and injected with hepatitis B immunoglobulin (HBIG). Many countries now routinely vaccinate infants against hepatitis B. In countries with high rates of hepatitis B infection, vaccination of newborns has not only reduced the risk of infection, but has also led to marked reduction in liver cancer. This was reported in Taiwan where the implementation of a nationwide hepatitis B vaccination program in 1984 was associated with a decline in the incidence of childhood hepatocellular carcinoma.

CONCLUSION

The present investigation suggested that the adjuvant therapy with hepatitis B vaccine together with lamivudine in chronic carriers of hepatitis B may lead to the eradication of viral infection in these patients. In addition, reduction in viral infections by lamivudine and recombinant hepatitis B vaccine is relatively a novel results, so the beneficial effect of lamivudine and recombinant hepatitis B vaccine could be the subject of further investigations.

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