RESEARCH

Immunogenicity of the Cuban anti-hepatitis B recombinant DNA vaccine in patients with Hematological Malignancies

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ABSTRACT

Parenteral-transmitted viral hepatitis is a significant health problem in persons with hematological malignancies that is why prevention measures against them are needed. One of the most important interventions is the prophylactic vaccination against hepatitis B virus infection. The results of a clinical trial using the Cuban antihepatitis B recombinant DNA vaccine in a group of adult patients belonging to 4 different chemotherapy status groups are shown. At 3, 12 and 18 months after the first dose the percentages of seroprotection were 63.33%, 72.66% and 78.33% respectively. There were differences in the immune response in relation to the treatment group. The geometric mean titre (GMT) at 3, 12 and 18 months was 46.53 IU/L (CI=23.57-67.36), 16.78 IU/L (CI=11.94-23.57) and 50.4 IU/L (CI=29.37-86.49) respectively. The Cuban antihepatitis B vaccine stimulates an acceptable immune response in adult patients with haematological malignancies preferably when it is started at the diagnosis and prior to the start of chemotherapy.

Key words: Anti-hepatitis B vaccine, DNA-recombinant vaccine, immunogenicity, hematological malignancies, clinical trial

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RESUMEN

Inmunogenicidad de la vacuna cubana ADN-recombinante contra la Hepatitis B en pacientes con enfermedades hematológicas malignas. Las hepatitis virales de transmisión parenteral son un importante problema de salud en los pacientes con enfermedades hematológicas malignas, de ahí la necesidad de incluir medidas de prevención contra ellas. Una de las intervenciones más importantes es la vacunación profiláctica contra la infección por el virus de la hepatitis B. Se presentan los resultados de un ensayo clínico con la vacuna cubana ADN-recombinante contra la hepatitis B en un grupo de pacientes adultos pertenecientes a 4 grupos diferentes de acuerdo al momento que se encontraban en relación con la quimioterapia. A los 3, 12 y 18 meses después de la 1ra. dosis, los porcentajes totales de seroprotección fueron 63.33%, 72.66% y 78.33% respectivamente, encontrándose diferencias en la respuesta inmune con relación al grupo de tratamiento. El título promedio geométrico (TPG) a los 3, 12 y 18 meses fue 46.53 UI/L (IC=23.57-67.36), 16.78 UI/L (IC=11.94-23.57) y 50.4 UI/L (IC=29.37-86.49) respectivamente. La vacuna cubana antihepatitis B estimula una respuesta inmune aceptable en pacientes adultos con hemopatías malignas, preferentemente cuando se suministra con el diagnóstico de la enfermedad y antes del comienzo de la quimioterapia.

Palabras claves: Vacuna anti-hepatitis B, vacuna ADN-recombinante, inmunogenicidad, hemopatías malignas, ensayo clínico

*I*ntroduction

Parenterally-transmitted viral hepatitis is considered a great health problem in persons with haematologic malignancies. Several factors may contribute to this: I) Repeated blood transfusions, receiving blood products and many other therapeutic and diagnostic percutaneus procedures, particularly in patients from developing countries with no programs of vaccination against hepatitis B and poor quality control of blood products. II) Immunosuppression in patients undergoing cancer chemotherapy places these subjects at a high risk of contracting and spreading the hepatitis B virus (HBV) which could even result in an endemic infection. III) Multidrug cancer chemotherapy may reactivate or worsen a previously benign chronic HBV infection. Immunosuppressants may impair T cell function and thereby reduce immune-mediated hepatocytolysis and virus clearance. In addition, corticosteroids promote HBV replication and gene expression; these effects frequently lead to persistently high viremia. [1, 2].

HBV infection can have a negative impact on the course of the disease and make its management even more difficult and costly. Thus, immunization against hepatitis B should be considered as a preventive measure to reduce the risk of HBV infection in these patients. However, some researchers argue that vaccination against HBV during cancer chemotherapy would not prevent the spread of the virus in oncology wards because it does not produce significant anti-HBs titers [3]. It has been reported that immunosuppression induced by both disease and treatment appears to diminish responsiveness to hepatitis B vaccination. Combining active and passive prophylaxis with vaccine and immunoglobulin

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respectively may be a more effective alternative in these patients [3].

This paper describes our experience in the assessment of immunogenicity of the Cuban Recombinant Hepatitis B vaccine (HEBERBIOVAC HB®) in patients with Hematological Malignancies.

Materials and methods

Subjects

The study was conducted at the Hematology-Oncology Unit of the Institute of Hematology and Immunology in Havana City, Cuba, from 1997 to 2000.

To learn the seroprevalence of HBsAg and anti-HBs in adult patients with haematologic malignancies we tested 139 adults (76 males and 63 females), with an average age of 41.02 years (ranging from 15 to 87 years). The diagnosis of this group of patients was as follows: 39 Acute Myeloblastic Leukemia, 37 Lymphomas, 26 Chronic Myeloblastic Leukemia, 17 Acute Lymphoblastic Leukemia, 8 Chronic Lymphoblastic Leukemia and all the others were unclassified Chronics Lymphoproliferative Syndromes.

Study inclusion criteria: Patients without HBV markers, and without previous vaccination against HBV.

According to this criterion, a total of 60 adults were included in the study. They received the Cuban recombinant hepatitis B vaccine (HEBERBIOVAC HB®) produced by the Center for Genetic Engineering and Biotechnology (CIGB), in Havana, Cuba. A 40-µg dose of the vaccine was injected into the deltoid muscle using the schedule of 0, 1, 2 and 12 months respectively.

Four groups of patients were considered according to the status of the chemotherapy:

Group I: before therapy (13 patients).

Group II: under intensive chemotherapy (17 patients).

Group III: under maintenance chemotherapy (18 patients).

Group IV: in remission and off therapy (12 patients).

A blood sample for the quantification of anti-HBs titers was drawn from each patient at 3, 12 and 18 months after the first dose of the vaccine. Sera samples were stored at -20 °C.

Methods

Titers of anti-HBs were measured using a commercially available test kit and equipment from TECNOSUMA International, Immunoassay Center, Havana, Cuba. Seroprotection was defined as anti-HBs titer of 10 IU/L or higher.

Ethical considerations

The informed consent was formally requested by the doctors.

Statistical analysis

The Anti-HBs geometric mean titer (GMT) with a 95% Confidence Intervals (CI) was calculated. The statistical differences between groups was assessed by Fisher's Exact Test.

Results and discussion

HEBERBIOVAC HB® is a yeast-derived recombinant DNA vaccine that only contains the HBsAg protein, so it was considered safe for administering to patients receiving immunosuppressive therapy. The safety of administering toxoids and inactivated vaccines to these patients is well documented. In contrast, the use of live vaccines must be managed carefully and the risk should be measured against demonstrable benefits in any vaccination program [1].

At 3, 12 and 18 months after the first dose, the number (percentage) of seroprotected patients was 38 (63.33%), 43 (71.66%) and 47 (78.33%) respectively (Figure 1).

Seroprotection was obtained in 78% of the immunized patients by the last of the four scheduled doses. This figure is lower than that previously reported of 100% seroprotection obtained with the same vaccine in healthy volunteers [4]. An explanation for this could be that they have an impaired cell-mediated immune response.

Our results are comparable with a previous study in Colombia with the same vaccine, where the authors obtained a seroprotection of 50.7 to 70.5% in children [5]. Another study in Turkey by Meral *et al.* reported 78% seroprotection with or without the fourth dose, and none of the children were infected with the HBV after 3 years of follow up [6]. However, Goyal and coworkers reported that only 10.5% of the patients had titers in the protective range using three doses of a recombinant DNA vaccine followed by a booster shot 1 year after the first dose [3].

Our data showed that at 12 months, just before the booster dose, seroprotection rate increased from 63% to 72%. Therefore, one could assume that it takes more time in these patients than in healthy people to reach adequate seroprotection rates.

The seroprotection rates at 3, 12 and 18 months in the chemotherapy group are shown in the Table 1. At 3 months, the group of patients under intensive chemotherapy (II) had the lowest percentage of seroprotected subjects, while the group of patients in

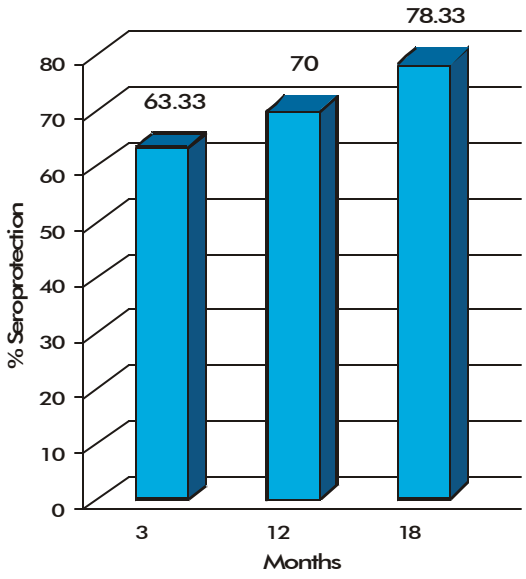

Figure 1. Seroprotection rates at 3, 12 and 18 months after the first dose.

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Table 1. Seroprotection rates at 3, 12 and 18 months according to the chemotherapy status group

Months	Group I (n=13)	Group II (n=17)	Group III (n=18)	Group IV (n=12)	Total (n=60)
3	8 (62%)	7 (41%)*	13 (72%)	10 (83%)*	38 (63%)
12	9 (69%)	11 (65%)	13 (72%)	10 (83%)	43 (72%)
18	9 (69%)	13 (76%)	15 (83%)	10 (83%)	47 (78%)

* Statistically significant differences $p < 0.05$

remission and off therapy (IV) had the highest percentage of seroprotected subjects. There are statistically significant differences between groups I and III ($p < 0.05$, unilateral test, $p1 < p2$). At 12 months, patients under intensive chemotherapy still had the lowest percentage of seroprotection. However, the percentage for these patients was higher than at 3 months. At 18 months, the only group with seroprotected subjects below 70% was that of patients that had not yet started chemotherapy. No statistically significant differences were found between the four groups at 12 and 18 months. In Groups II and III seroprotection rates increased at the end of the vaccination schedule, whereas in Groups I and IV they remained constant at 12 and 18 months.

Many studies conducted in children with hematological malignancies as well as with solid tumors during different stages of chemotherapy not always have the same seroprotection rates to Hepatitis B vaccination. Berberoglu *et al*. obtained seroconvertion rates of 70.7% at 12 months after vaccination in children with cancer following diagnosis [7]. Ramesh and coworkers obtained only 28.6% protective titers in children receiving cancer chemotherapy. Moreover, they reported that some patients lose their protective titers during the course of intensive therapy [8]. In our study the seroprotection rates increased with dose administration in groups II and III and no patients lost their titers. Rokicka-Milewska *et al.* has postulated that children vaccinated during the maintenance treatment did not show protection against infection [9]; however, we obtained on 83% seroprotection rate in Group III. Another study conducted in Greece reported an overall seroconvertion rate 1 month after the fourth dose of 57%. The highest protective anti-HBs titer was observed in children under complete remission and off treatment compared to those undergoing cancer chemotherapy [10].

At the end of the study (18 months) the group of patients that had not started chemotherapy had the worse seroprotection response. We believe that by this time the immunosuppression induced by the disease could have hampered sero-responsiveness. This may suggest that the vaccine should be administered as soon as the diagnosis of the hematological malignancy is confirmed and before therapy is started.

Studies conducted in immunocompromised subjects such as HIV/AIDS patients and those undergoing hemodialysis with HEBERBIOVAC HB®, have obtained results similar to those with hematological malignancies. In the case of HIV/AIDS patients vaccinated with 3 doses of HEBERBIOVAC HB®, the authors showed a seroprotection rate of 63.4% for the subjects in CDC groups 2, 3, 4B, 4C2 and 4E, whereas the rate was 37.5% for subjects in CDC groups 4ª, 4C1 and 4D. The booster dose at 12 months increased seroprotection rates in the former group, but not in the latter one [11]. The administration of the vaccine showed a seroprotection rate of 89% when administered to patients undergoing hemodialysis or peritoneal dialysis under a schedule of 0, 1, 5, 6 and 12 months and a dose of 40 µg. These patients have a Prevention Program that indicaties vaccination during the kidney disease, just before starting the treatment at the hemodialysis unit [12].

Moreover, the anti-HBs Geometric Mean Titers (GMT) with 95% Confidence Intervals (CI) attained at 3, 12 and 18 months were 46.53 IU/L (CI = 23.57-67.36), 16.78 IU/L (CI = 11.94-23.57) and 50.4 IU/L (CI = 29.37-86.49) respectively.

In the present study, anti-HBs GMT obtained at 3, 12 and 18 months were under 100 IU/L, which is considered to be a low response (hyporesponse).This may be due to the light immunodepressed condition of most of these patients. The GMT at 12 months was somewhat lower than the GMT at 3 and 18 months. This may result from the sera sample being drawn on the same day the 12 month booster dose was administered. This may emphasize the importance of the booster dose in this particular group of patients.

In the literature, certain authors have reported higher GMT. Rokicka-Milewska et al. showed that 1 year after primary vaccination, most of the immunized children had titers above 1000 mlU/L [9]. On the other hand, Berberoglu *et al.* in children with cancer achieved GMT of 212 and 373 mlU/L at 9 and 12 months respectively [7].

These results suggest that HEBERBIOVAC HB®, a recombinant DNA hepatitis B vaccine, stimulates an acceptable humoral immune response in adult patients with haematologic malignancies, whose immunological responses are considered compromised. More than 75% of these patients may potentially show a satisfactory immune response. Vaccination may induce a more seroprotective response when it is started just after the diagnosis of the hematological malignancy and preferably before starting chemotherapy. Recommendations for booster shots should await follow-up data over a longer period of time.

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