Prevalence of protective antibody against hepatitis B virus in HIV-infected children with immune recovery after highly active antiretroviral therapy

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Abstract

HIV-infected children had a lower seroconversion rate to hepatitis B immunization and a more rapid antibody decline when compared to healthy children. Whether re-immunization or additional booster dose is necessary after immune recovery remains unknown. This study was conducted to determine the prevalence of hepatitis B virus protective antibody in HIV-infected children with immune recovery after highly active antiretroviral therapy (HAART). Serum hepatitis B viral markers were measured. An antibody level of \( \geq 10 \) mIU/mL was defined as a protective antibody level. Only one out of 69 children (1%) had a protective antibody level. We concluded that despite the history of hepatitis B immunization and despite evidence of immune recovery after HAART, most HIV-infected children are still susceptible to HBV infection.

Keywords: Hepatitis B virus (HBV); Human immunodeficiency virus (HIV); Protective antibody

1. Introduction

Experience from studies involving hematopoietic stem cell transplantation (HSCT) recipients revealed that protective immunity to diseases preventable by routine vaccination was lost over time following transplantation. Furthermore, adoptive transfer of immunity from donors to recipients after allogeneic transplantation was not sufficient to prevent this decline. Systematic re-immunization was necessary at appropriate time intervals following transplantation to re-establish immunity [1]. Consequently, the Centers for Disease Control and Prevention (CDC), the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation have published evidence-based recommendations, including re-immunization schedules, for preventing of opportunistic infections among HSCT patients [2].

Human immunodeficiency virus (HIV) infection destroys CD4 cells which provide critical help to B cells in the production of antibodies against T cell-dependent antigens and in the differentiation of B cells into memory cells [3]. Previous studies had suggested that combination antiretroviral therapy can stop CD4 cell attrition and at least partially restore the immune system [4]. This restoration may include immune responses to childhood vaccines. The current World Health Organization recommendations for immunization of children with known or suspected HIV infection is based on the degree of HIV-induced immunosuppression [5]. But guidelines for HIV-infected children with immune recovery after highly active antiretroviral therapy (HAART) have not yet been established.

Hepatitis B virus (HBV) infection is a major public health problem in Thailand. The estimated prevalence of HBV carriage is 8–12% in males and 4–8% in females [6]. There is also a high prevalence of 1–2% of HIV infection among
remained above 90% \[\text{after vaccination}\]. The decline in antibody level in non-HIV infected children was from 77.8 to 23.1% within 2 years \[\text{of vaccination}\]. It has been shown that the prevalence of protective antibody level in HIV-infected children was detected in only 42% of these children who had seroconverted after primary series \[\text{[13]}\]. Zain et al. have shown that the prevalence of protective antibody level in HIV-infected children declined from 77.8 to 23.1% within 2 years \[\text{after vaccination}\], whereas that in a non-HIV-infected group \[\text{[14]}\]. A study in Thailand revealed the seroconversion rate at 6 months after vaccination to be 71.4% in HIV-infected infants compared to 91.9% in the non-HIV-infected group \[\text{[14]}\]. Furthermore, a more rapid serum antibody decline has also been reported. At 13 months after vaccination, protective antibody level was detected in only 42% of HIV-infected children who had seroconverted after primary series \[\text{[13]}\]. Zain et al. have shown that the prevalence of protective antibody level in HIV-infected children declined from 77.8 to 23.1% within 2 years \[\text{after vaccination}\]. The introduction of HAART has resulted in prolonged survival of HIV-infected children. However, information about the long-term persistence of antibody to hepatitis B surface antigen (anti-HBs Ab) after vaccination in these children is limited. Whether re-immunization or additional booster dose is necessary and effective after immune recovery remains unknown. Because of low seroconversion rate and rapid antibody decline over time, we hypothesized that most HIV-infected children have a non-protective antibody level and consequently have increased susceptibility to breakthrough HBV infection even after the commencement of HAART. Thus, we conducted this study to determine the prevalence of HBV protective antibody in HIV-infected children with immune recovery after HAART.

2. Patients and methods

This cross-sectional study was conducted at Chiang Mai University hospital in March 2005. The study protocol was approved by the research ethics committee of Chiang Mai University. Written informed consent was obtained from each child’s parent or guardian before enrollment. The inclusion criteria were HIV-infected children who: (1) were more than 5 years of age, (2) had been severely immunosuppressed (CD4 cell < 15%), (3) received HAART which was defined as ≥3 antiretroviral drugs in a regimen in which ≥1 of antiretroviral drugs was a protease inhibitor or a nonnucleoside reverse-transcriptase inhibitor, (4) had shown evidence of immune recovery for at least 3 months after HAART (CD4 cell ≥ 15%), and (5) had had their HBV immunization documented in the medical records or by interview with caregivers. The exclusion criteria were children who: (1) received immunosuppressive agents within 3 months, or (2) received blood component transfusion within 6 months prior to the study. Past illnesses and immunization data were collected by medical record review and caregiver interview. The clinical stage of disease was determined according to the 1994 US CDC revised classification \[\text{[16]}\].

The serial CD4 cell count and plasma HIV RNA level were routinely performed in HIV-infected children at the beginning of HAART and at every 3–6 months afterward. CD4 cell counts and percentages were assessed with the use of a FACSCount apparatus (Becton-Dickinson). Plasma HIV RNA levels were measured by the Roche Ultrasensitive Amplicor assay, version 1.5 (Roche). The most recent values of CD4 cell count and plasma HIV RNA level obtained within 3 months before or after the study were designated as current values in this report.

Blood samples were collected for HBV profiles. Serum hepatitis B surface antigen (HBsAg), anti-HBs Ab, and antibody to hepatitis B core antigen (anti-HBc Ab) were measured by HBsAg (V2), AUSAB\textsuperscript{TM}, and CORE\textsuperscript{TM}, enzyme-linked immunosassay diagnostic kits (Abbott Laboratories, Abbott Park, IL, USA), respectively. The amount of anti-HBs Ab was determined using the calibration curve generated by AxSYM AUSAB. An antibody level of ≥10 mIU/mL was defined as a protective antibody level. The children who had either HBsAg or anti-HBc Ab were considered to have natural HBV infection \[\text{[17]}\]. The chronic carrier state of children with HBsAg and no anti-HBs Ab was confirmed by persisting serum HBsAg 6 months after the first test \[\text{[17]}\]. The liver function profiles of these carriers were done to determine whether active hepatitis was present. Statistical analyses were performed with Statistical Package for Social Science version 11.5 software (SPSS Inc., Chicago, IL, USA).

3. Results

Seventy-five HIV-infected children were enrolled. The demographic data and immunological and viral status of the participants are shown in Table 1. There were 39 boys and 36 girls. The mean age was 9.6 years (S.D. = 2.5). Half of them (51%) were in CDC clinical category C. Means of CD4 cell percentage and plasma HIV RNA level prior to initiation of HAART were 5% (S.D. = 5) and 5.4 log\textsubscript{10} copies/mL (S.D. = 0.4), respectively. Means of current CD4 cell percentage and plasma HIV RNA level were 25% (S.D. = 5) and 1.8 log\textsubscript{10} copies/mL (S.D. = 0.5), respectively. There were only six children (8%) whose current HIV RNA levels were more than 1.7 log\textsubscript{10} copies/mL. The mean age at which HAART was prescribed was 7.6 years (S.D. = 2.5). They had been treated with HAART for an average of 2 years and
Table 1
Characteristics of study participants (N=75)  

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>9.6 ± 2.5</td>
</tr>
<tr>
<td>Male (gender)</td>
<td>39(52)</td>
</tr>
<tr>
<td>CDC clinical category</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>7(9)</td>
</tr>
<tr>
<td>A</td>
<td>(5±20)</td>
</tr>
<tr>
<td>B</td>
<td>(5±20)</td>
</tr>
<tr>
<td>C</td>
<td>38(51)</td>
</tr>
<tr>
<td>CD4 cell percentage prior to HAART (%)</td>
<td>5 ± 5</td>
</tr>
<tr>
<td>Plasma HIV RNA level prior to HAART (log10 copies/mL)</td>
<td>5.4 ± 0.4</td>
</tr>
<tr>
<td>HAART regimen</td>
<td></td>
</tr>
<tr>
<td>Nevirapine-baseda</td>
<td>35(47)</td>
</tr>
<tr>
<td>Efavirenz-baseda</td>
<td>35(47)</td>
</tr>
<tr>
<td>Protease inhibitor-baseda</td>
<td>5(6)</td>
</tr>
<tr>
<td>Current CD4 cell percentage (%)</td>
<td>25 ± 5</td>
</tr>
<tr>
<td>Current plasma HIV RNA level (log10 copies/mL)</td>
<td>1.8 ± 0.5</td>
</tr>
<tr>
<td>Age at which HAART was prescribed (years)</td>
<td>7.6 ± 2.5</td>
</tr>
<tr>
<td>Duration of HAART (months)</td>
<td>24.0 ± 4.4</td>
</tr>
<tr>
<td>Duration of documented severe immune suppression (CD4 cell &lt;15%) (months)</td>
<td>14.1 ± 6.7</td>
</tr>
<tr>
<td>Duration of documented immune recovery (CD4 cell ≥15%) (months)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Data are shown in number (%) or mean ± S.D.
* A combination of two nucleotide reverse transcriptase inhibitors with nevirapine, efavirenz, or a protease inhibitor.

their CD4 cell percentage had been ≥15% for more than 1 year.

The HIV immunization status was documented by medi-
cal record in 55 children (73%) and by history in 20 children (27%). There was no difference in baseline characteristics
between the two groups except that the former group have
received HAART slightly longer (24.6 ± 4.4 months ver-
sus 22.2 ± 4.2 months, p = 0.033). Fifty-three of 55 chil-
dren whose immunization status was documented by medical
record received a three-dose regimen (at birth, 2 months, and
6 months of age), while the remaining two children received
a four-dose regimen (at birth, 2 months, 6 months, and 12
months of age).

As Fig. 1 indicates, 69 children (92%) did not have evi-
dence of natural HBV infection. Only one (1%) had protective
level of anti-HBs Ab. Fifteen children (20%) had low levels
of anti-HBs Ab and 53 children (71%) had undetectable lev-
els of anti-HBs Ab. Among six children who had evidence of
natural HBV infection, two (3%) also had persisting HBsAg
and were classified as chronic HBV carriers. They had no
history of clinical hepatitis. Current liver function profiles
were within normal limits. They had no history of blood
transfusion. There was no information on the HBV status of
the mothers of these two children. Two of the remaining
four (3%) developed naturally acquired immunity while
another two did not. Among three children who had pro-
tective antibody levels, the one who had vaccine-induced
immunity had a lower anti-HBs Ab level than the other two
children who had natural infection (11.1 mIU/mL versus 25.5
and 1000 mIU/mL).

Maternal hepatitis B status was available in only three
children. Two of the mothers had positive HBsAg and the
newborns were given hepatitis B vaccine and hepatitis B
immune globulin (HBIG) within 12 h after birth. Neither of
them acquired HBV infection through perinatal transmission.
Nine children (12%) had history of blood transfusions but
their most recent transfusions were more than 6 months prior
to the study. None of them acquired HBV infection through
blood transfusion.

Of the two children who received a four-dose regimen of
HBV immunization, one had an undetectable anti-HBs Ab
level while the other had evidence of breakthrough infection
with a low anti-HBs Ab level.

4. Discussion

In the present study, we found that the prevalence of HBV
protective antibody in HIV-infected children with immune
recovery after HAART was as low as 1%. The result con-
formed our hypothesis that most HIV-infected children with
immune recovery after HAART are susceptible to HBV
infection despite HBV immunization during the infancy
period. Further study is required to determine whether re-
immunization or additional booster dose will result in pro-
tective levels of anti-HBs Ab in this population.

In our study, the percentage of children who had anti-HBs
Ab ≥10 mIU/mL was found to be 4% (three children), while
two of these three children developed naturally acquired
immunity. In a study in healthy Italian children who received
a three-dose primary HBV immunization during infancy
period, the anti-HBs Ab remained above protective level in
64% 10 years after the immunization [18]. The difference
between the persistence of HBV protective antibody among
HIV-infected and healthy children may be explained either by
low seroconversion rate to the primary series (primary vac-
cine failure) [13–15] or by the more rapid rate of antibody
decline (secondary vaccine failure) [13–15].

Of the 69 children in this study who did not have evidence
of natural HBV infection, only one developed a protective
anti-HBs Ab level from immunization. All six children who
had shown evidence of natural HBV infection had no his-
tory of clinical hepatitis. Two of these six (33%) had turned
into chronic carrier stage. This supported the finding from
a previous study which demonstrated that HIV-infected sub-
jects co-infected with HBV had a higher progression rate to
chronic disease [8].

Factors that might affect immune responses to primary
HBV immunization in HIV-infected children have been stud-
ied [11,13–15]. The CD4 cell count, clinical category, and age
at first vaccination were not significantly different between
children who were able to mount an immune response to
HBV vaccine and those who were not. In our study, there
was only one child who had vaccine-induced immunity, so
the factors affecting immune response to HBV vaccine cannot be addressed.

Findings in immunocompetent persons suggested that routine boosters were not necessary due to anamnestic antibody responses that followed exposure to HBV, even when antibodies had declined to low or undetectable levels [19,20]. This finding may not be applicable to immunocompromised persons. In HSCT recipients, the CDC recommended HBV re-immunization with the usual dosage of vaccine at 12, 14, and 24 months after transplantation, and post-vaccination anti-HBs Ab testing at 1–2 months after the third dose. Persons who do not respond to this primary vaccine series should complete a second three-dose series [2]. In studies in HIV-infected adults the majority of whom were receiving HAART, the response rates to HBV immunization were 34–47% [21,22]. Whether one should apply similar measures in HIV-infected children whose immune system had been restored by HAART should be further investigated.

There were several limitations in this study. First, because of the cross-sectional study design, there was no information on the baseline primary antibody response to HBV vaccine in order to address the issue of primary versus secondary vaccination failure. Secondly, 27% of the past HBV immunization was determined by history taking. Normally in Thailand, vaccination history was documented in the medical record and in the patient’s copy of the vaccination book. The medical records were kept only for 5 years after last visit. Despite efforts to contact the children’s health care providers and family members, we could not obtain either medical records or vaccination books for the infancy period of these children.

In conclusion, we have documented low prevalence of HBV protective antibody in HIV-infected children with immune recovery after HAART, despite HBV immunization during infancy. Further study is required to determine whether re-immunization or additional booster dose will protect these children against HBV infection.

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References