CONCISE COMMUNICATIONS

Immunogenicity and Safety of Hepatitis A Vaccine in Liver and Renal Transplant Recipients

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Organ transplant recipients with chronic hepatitis B or hepatitis C virus infection may be at increased risk of fulminant hepatitis A. Liver transplant (LTX) recipients, renal transplant (RTX) recipients, and healthy controls received 2 doses of hepatitis A vaccine 6 months apart. Anti–hepatitis A virus (anti-HAV) seroconversion after the primary dose occurred in 41% of the LTX patients, 24% of the RTX patients, and 90% of the controls. After the booster dose, the respective rates were 97%, 72%, and 100% ($P < .001$). RTX patients also had significantly lower geometric mean titers (GMTs) of anti-HAV than LTX patients and controls. In the RTX group, the seroconversion rate and GMT were inversely associated with the number of immunosuppressive drugs received by the patients. The vaccine was well tolerated. Hepatitis A vaccine can be recommended to LTX and RTX patients, but the patients should receive a full course of 2 doses before imminent exposure.

Hepatitis A is common in the developing world and in many industrialized countries. In several industrialized countries, large hepatitis A outbreaks or increases in the total number of cases have been reported recently [1, 2]. Hepatitis A virus (HAV) infection rarely causes fulminant hepatic failure. In a sentinel surveillance in the United States, the case fatality rate was 0.2% among all hepatitis A patients [1]. This risk increases with age, and there is mounting evidence that fulminant hepatitis A occurs more often in individuals with chronic liver disease [3, 4]. In one study, the hepatitis A case fatality rate was 11% among chronic hepatitis B surface antigen carriers [3]. In another study, hepatitis A resulted in fulminant hepatic failure in 41% of the patients with chronic hepatitis C virus (HCV) infection and was fatal in 35% of them [4].

In many countries, organ transplant recipients have significantly higher prevalences of chronic hepatitis B virus (HBV) and HCV infection than the general population [5, 6]. Hepatitis may be the underlying disease leading to transplantation, or it may have been acquired during long periods of hemodialysis in renal transplant (RTX) recipients or as a consequence of frequent blood transfusions before anti-HCV testing of blood products became mandatory. Transplant recipients with chronic HBV or HCV infection would benefit most from the inactivated hepatitis A vaccine, which has been shown to be immunogenic and safe in immunocompetent individuals [7]. For other transplant patients, the vaccination may also be indicated because of high risks of exposure (e.g., travel to areas where HAV is endemic). In organ transplant recipients, the immunogenicity of most routine vaccinations is significantly lower than that in healthy adults, but relatively good immunity levels are achieved with tetanus, diphtheria, and influenza vaccines [8–10].

Data on the immunogenicity of hepatitis A vaccine in immunocompromised individuals are scarce. A few studies were done in HIV-infected individuals or in patients with chronic liver disease [11, 12]. However, to our knowledge, no data are available on the immunogenicity and safety of hepatitis A vaccine in liver transplant (LTX) or RTX recipients.

Methods

Study population. LTX and RTX recipients ≥18 years old who were seronegative for anti-HAV and anti–human immunodeficiency virus were recruited from the transplantation outpatient units of the Departments of Internal Medicine and Surgery at the University Hospital Charité, Campus Virchow, Humboldt University. The healthy controls were employees of the Berlin city council who had been anti-HAV–seronegative in a screening test (Sorin, Düsseldorf, Germany). Baseline data on age, sex, time since transplantation, and immunosuppressive treatment (type and number of drugs) were obtained by administration of standardized questionnaires. Local and general symptoms during the first 3 days after the vaccination were

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Informed consent was obtained from all patients, and the guidelines of the ethics committee of the Medical Faculty Charité, Humboldt University, were followed.

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Table 1. Anti–hepatitis A virus (anti-HAV) response following vaccination with hepatitis A vaccine in initially anti-HAV–seronegative liver transplant (LTX) patients, renal transplant (RTX) patients, and healthy controls.

Variable	LTX patients (n = 39)	RTX patients (n = 39)	Controls (n = 29)	P
No. (%) responding				
After dose 1	16/39 (41.0)	9/38 (23.7)	26/29 (89.7)	<.0001
After dose 2	37/38 (97.4)	28/39 (71.8)	27/27 (100)	<.001
GMT (95% CI)[a]				
After dose 1	101 (33–164)	17 (11–26)	169 (97–313)	—[b]
After dose 2	1306 (560–2903)	85 (48–151)	1596 (1093–2652)	—[c]

[a] GMT, geometric mean titer, in mIU/mL; CI, confidence interval.
[b] RTX vs. LTX, $P < .01$, $z = -2.8$; LTX vs. controls, $P < .05$, $z = -2.2$; RTX vs. controls, $P < .0001$, $z = -5.7$ (Mann-Whitney test).
[c] RTX vs. LTX, $P < .0001$, $z = -5.2$; LTX vs. controls, $P = .35$, $z = -0.9$; RTX vs. controls, $P < .0001$, $z = -5.8$ (Mann-Whitney test).

recorded by the patients. Any additional adverse events reported to the physicians were documented as well. The patients did not experience any rejection episodes during the 3 months prior to the first vaccine dose.

Vaccination and specimen collection. The hepatitis A vaccine contained 1440 ELISA units of inactivated HM175 HAV per each 1-mL dose (Havrix 1440; SmithKline Beecham, Rixensart, Belgium). The participants received 2 doses of hepatitis A vaccine 6 months apart. The vaccine was administered in the deltoid muscle. A blood sample was obtained before the primary dose was given, and further samples were obtained 1 month after each dose. The sera were stored at −70°C until they were tested for HAV antibodies.

Anti-HAV testing. Anti-HAV titers were determined by use of a commercially available ELISA (Boehringer Enzymun kit; Boehringer Mannheim, Mannheim, Germany), which was calibrated by use of World Health Organization international standard reference serum and expressed in mIU/mL. Subjects with titers <33 mIU/mL were considered seronegative.

Statistical analysis. For comparisons of proportions between groups, the χ^2 test or Fisher's exact test was used. For comparisons of quantitative variables, the t test or the Mann-Whitney U test was applied as appropriate. Geometric mean titers (GMTs) of anti-HAV were calculated. The log-transformed antibody titers for 2 groups were compared by use of the Mann-Whitney U test. Associations between quantitative variables were assessed by correlation and linear regression. A P value of .05 was considered statistically significant. Logistic regression analysis was done to identify independent predictors of the outcome "seroconversion yes/no." The variables included in the regression models as explanatory variables or confounders were patient group, age, sex, time since transplantation, and number of immunosuppressive drugs. The model that gave the best fit, as indicated by the likelihood ratio statistic, was chosen as the final model.

Results

Overall, 107 persons were entered into the study (39 LTX patients, 39 RTX patients, and 29 controls), and 104 completed the full vaccine course. With a mean age of 48.3 years (SD, 9.8), the LTX patients were significantly older than the RTX patients (mean age, 42.5 ± 11.4 years) and the controls (mean age, 40.9 ± 10.2 years; $P < .05$). Of the controls, 69% were women, compared with 50% of all transplant recipients ($P < .05$). Most of the LTX patients received either tacrolimus (45%) or cyclosporin A (43%) for immunosuppressive treatment, whereas all RTX patients received combinations of ⩾2 immunosuppressive drugs. In this group, the most common combinations were cyclosporin A/azathioprine/prednisolone (41%), azathioprine/prednisolone (27%), and cyclosporin A/prednisolone (15%). The median time interval since transplantation was 40 months (interquartile range [IQR], 22–74 months) among the LTX and 96 months (IQR, 78–139 months) among the RTX patients ($P < .001$). Of the LTX patients, 41% had undergone transplantation because of chronic HBV or HCV infection. Of the RTX patients, 10% had serologic evidence of chronic HBV infection, and 28% had serologic evidence of chronic HCV infection.

Anti-HAV response. Anti-HAV seroconversion after the first dose occurred in 41% of the LTX patients, 24% of the RTX patients, and 90% of the controls ($\chi^2 = 29.9$, $P < .0001$). One month after the second dose, 97% of the LTX patients, 72% of the RTX patients, and 100% of the controls had seroconverted ($P < .001$ for comparison between RTX and LTX patients [$\chi^2 = 9.6$] and between RTX patients and controls [$\chi^2 = 16.7$]; table 1).

Similar results were observed with respect to the anti-HAV GMTs (table 1). After the second dose, the RTX patients had significantly lower GMTs than the LTX patients and controls (table 1). When only the seroconverters were considered, again no GMT differences after the second dose were observed between the LTX group (GMT = 2259 mIU/mL) and controls (GMT = 1850 mIU/mL), but the RTX group had significantly lower titers (GMT = 290 mIU/mL; $P < .0001$).

In the total study population, women had a higher seroconversion rate than men (93% vs. 83%; $\chi^2 = 2.8$, $P = 0.1$) and a significantly higher GMT after the second vaccine dose (818 vs. 260 mIU/mL, $P < .01$). Neither the seroconversion rates nor

the GMTs were associated with age, time interval since transplantation, or HBV or HCV serostatus.

The seroconversion rates and GMTs after the second dose were significantly higher in patients receiving immunosuppressive monotherapy than in patients with double or triple therapy (GMTs = 1340 mIU/mL for monotherapy, 136 mIU/mL for double therapy, and 88 mIU/mL for triple therapy; $P < .0001$, Kruskal-Wallis test). When data were analyzed separately for the RTX group, the seroconversion rates and GMTs after the booster dose were higher in patients receiving double therapy than in those receiving triple therapy. In the RTX seroconverters, the anti-HAV GMT after 2 doses was 296 mIU/mL in the double therapy group ($n = 11$) and 117 mIU/mL in the triple therapy group ($n = 17$; $P = .05$).

After we adjusted for age and sex in logistic regression, the RTX patients (in comparison with the LTX patients at baseline) had an odds ratio for the outcome "seroconversion after 2 vaccine doses" of 0.15 (95% confidence interval, 0.03–0.6). Sex was no longer associated with anti-HAV seroconversion.

Safety. The most common side effects were tenderness at the site of injection (33%), mild fatigue (14%), headache (10%), and fever (3%). Side effects occurred less frequently among the organ transplant recipients. However, this did not reach statistical significance. No serious adverse events were observed. The side effects were evenly distributed with respect to the first and second vaccine dose.

Discussion

In our study, most LTX patients (97%) and all controls developed protective anti-HAV titers after 2 doses of hepatitis A vaccine. The results were not as satisfactory in the RTX group, but 72% of these patients did have protective HAV antibodies after the booster dose. The differences between the LTX and the RTX patient groups were even more pronounced with respect to the GMTs.

In a previous study, it was estimated on the basis of follow-up data from healthy adult vaccinees that protection after a full course of hepatitis A vaccine may last for at least 20–30 years [7]. However, in organ transplant recipients, and especially in those with low postvaccination titers, anti-HAV titers may decline much faster and may be undetectable after a few years. It is unclear whether immunity still persists in these cases [13]. Studies are needed to assess the postvaccination HAV antibody decline in immunocompromised patients and to define the time when booster vaccinations may be necessary.

In most transplant recipients (68%), a single vaccine dose did not afford protection. This is in contrast to healthy individuals, among whom the seroconversion rate after the primary dose is usually >90%. The policy that individuals are vaccinated only once before they travel to areas endemic for hepatitis A is inadequate for transplant recipients. These individuals should receive the full course of 2 doses before exposure.

In another study among patients with chronic HBV or HCV infection who had not undergone transplantation [12], significantly higher seroconversion rates after the primary dose were achieved than those achieved in our study. However, after 2 doses, the seroconversion rate was similar to that in our LTX patients. In a study among HIV-infected homosexual men, the seroconversion rate after the full vaccine course was 64% in individuals with CD4 cell counts $\leqslant 200/\mu L$, which is similar to the figure in our RTX patients [11].

We and others (e.g., Keeffe et al. [12]) used a cutoff anti-HAV titer of 33 mIU/mL to define "seropositive." This may result in a somewhat lower sensitivity than that found in studies with a cutoff of 20 mIU/mL. Applying this lower cutoff, however, would not have changed our results substantially, because only 1 person in the LTX and RTX groups had titers between 20 and 33 mIU/mL. The protective anti-HAV level remains to be defined.

Impairments of the humoral and cellular immune responses in organ transplant recipients obviously result in postvaccination anti-HAV titers lower than those of healthy controls. The differences in vaccine immunogenicity between LTX and the RTX patients may be due in part to differences in immunosuppressive treatment that result in a higher degree of immunosuppression in the RTX patients. Because of the colinearity between transplant type and number of immunosuppressive drugs, it cannot be decided which of the factors determines the immune response. When we restricted the analysis to the RTX group, the patients undergoing triple therapy had a lower GMT than those receiving double therapy. This suggests that the type of immunosuppressive treatment may influence the response after vaccination. On the other hand, in RTX patients, a monocyte/B cell defect independent of the type and dosage of immunosuppressive treatment has been reported [14].

Hepatitis A vaccination is already recommended in some countries to patients with chronic liver disease. Our study shows that hepatitis A vaccine is safe and immunogenic in LTX patients who should be protected from any further liver injury due to hepatitis A. Moreover, RTX patients and other organ transplant recipients also benefit from the vaccine if they have chronic HBV or HCV infection or if they are highly exposed to hepatitis A.

Further studies are needed to elucidate the determinants of the immune response after hepatitis A vaccination (immunogenetic host characteristics, type of immunosuppressive treatment, immune dysfunction). Future research should also investigate the immunogenicity and safety of alternative vaccination regimens (e.g., higher vaccine dosage for immunocompromised patients).

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