Early Introduction of Subcutaneous Hepatitis B Immunoglobulin Following Liver Transplantation for Hepatitis B Virus Infection: A Prospective, Multicenter Study

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Background. Subcutaneous administration of hepatitis B immunoglobulin (HBIg) is effective in preventing hepatitis B virus (HBV) recurrence after liver transplantation, but early conversion to subcutaneous administration is undocumented. Methods. In a prospective study, patients transplanted for terminal liver disease due to HBV infection who were HBV DNA-negative at transplant were switched by week 3 posttransplantation from intravenous to subcutaneous HBIg (500 or 1000 IU weekly or fortnightly, adjusted according to serum anti-HBs trough level) if they were HBsAg- and HBV DNA-negative at time of switch. All patients concomitantly received nucleos(t)ide analogue antiviral therapy. Primary endpoint was failure rate by month 6, defined as serum anti-HBs of 100 IU/L or less or HBV reinfecion despite serum anti-HBs greater than 100 IU/L. Results. Of 49 patients treated, 47 (95.9%) continued treatment until month 6. All patients achieved administration by a caregiver or self-injection by week 14. No treatment failures occurred. Mean anti-HBs declined progressively to month 6, plateauing at a protective titer of approximately 290 IU/L. All patients tested for HBV DNA remained negative (45/45). Only 1 adverse event (mild injection site hematoma) was assessed as treatment-related. Conclusions. Introduction of subcutaneous HBIg administration by week 3 posttransplantation, combined with HBV virostatic prophylaxis, is effective and convenient for preventing HBV recurrence.

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The introduction of regular intravenous administration of hepatitis B immunoglobulin (HBIG) for hepatitis B virus (HBV) reinfection prophylaxis in the early 1990s led to a dramatic reduction in HBV recurrence after liver transplantation such that 5-year survival following transplantation now approaches 80%-85%. Combination prophylaxis with HBIG and nucleoside or nucleotide antiviral drugs is more effective than either treatment alone and is generally considered the standard of care in at-risk patients, although routine use of HBIG is not universal. Low-dose or fixed-term intravenous HBIG regimens have been widely adopted following evidence that efficacy is preserved with significant cost savings compared with early high-dose protocols. Some centers instead use intramuscular administration of HBIG, which again maintains efficacy at a lower cost than conventional intravenous regimens. Most intramuscular HBIG products, however, are not licensed for prevention of HBV reinfection, and the intramuscular route is contraindicated in patients with coagulopathies or who are receiving oral anticoagulant therapy, as well as being painful to administer.

Subcutaneous administration of HBIG in combination with antiviral therapy is an appealing alternative that offers patients the option to self-administer at home. A randomized, single-dose trial in healthy volunteers has confirmed that the pharmacokinetics of HBIG are similar using either subcutaneous or intramuscular injection. Clinical studies have shown that the serum anti-HBs concentration remains above 100 IU/L in patients treated with subcutaneous HBIG, a threshold regarded as the minimum for effective prevention of HBV reinfection in HBV-DNA-negative patients, with few adverse events. Previous studies, in which patients were switched from intravenous to subcutaneous HBIG have usually undertaken the conversion at 6 months posttransplantation or later. However, it would be convenient for patients if the transition to subcutaneous HBIG could be undertaken during the initial hospital stay, avoiding the need for additional clinic visits and patient training by nursing staff in the ambulatory departments. Data on early switch to subcutaneous administration are sparse.

The aim of the current study was to assess the prevention of HBV reinfection in HBV-DNA-negative liver transplant patients after initiation of subcutaneous HBIG by week 3 posttransplantation.

**MATERIALS AND METHODS**

**Study Design and Conduct**

This was a prospective, open-label, single-arm, phase III, 6-month study in which patients undergoing liver transplantation due to HBV infection were switched from intravenous HBIG to subcutaneous administration by week 3 posttransplantation. The study was conducted at 17 centers in Italy, Spain, France, and the United Kingdom during December 2012 to September 2014.

The study protocol was approved by the institutional review board at each site and was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. All participants provided written informed consent.

**Patient Population**

Patients aged 18 to 75 years undergoing a first or subsequent liver transplantation due to HBV infection were eligible to enter the study if they met the following criteria: HBV-DNA negative at time of transplant and at the time of switch to subcutaneous HBIG; HBsAg negative with serum HBs antibody concentration of 400 IU/L or greater at week 1 or 2 posttransplantation, that is, the time of switch to subcutaneous administration and stable clinical condition in the opinion of the investigator. Patients were converted to subcutaneous HBIG as soon as they became HBsAg-negative, if serum HBs antibody concentration is 400 IU/L or greater. The threshold of 400 IU/L was selected to ensure an adequate safety margin above 100 IU/L, considering the minimum for effective HBV reinfection prevention. The key exclusion criteria were retransplantation due to viral recurrence, positive HIV, or hepatitis C test at time of transplant, and a donor positive for HBsAg. Patients positive for hepatitis D virus could be enrolled, as could patients without liver failure who underwent transplantation because of hepatocellular carcinoma due to hepatitis B infection.

**Study Treatment**

Patients who met the eligibility criteria were converted from intravenous standard HBIG to subcutaneous HBIG (Zutectra; Biotest AG, Dreieich, Germany) at approximately days 8 to 11 or 15 to 18 posttransplantation, according to their HBsAg status, that is, switch took place as soon as the patient’s serum became free of HBsAg from day 8 onward. Subcutaneous HBIG was administered once a week or once every 2 weeks, at the discretion of the investigator, until month 6 posttransplantation at a maximum dose of 1000 IU (2 mL). The dose was adjusted based on the serum anti-HBs concentration, at the discretion of the study investigator. In exceptional cases, a dose of up to 1500 IU/L was permissible. In the event of serum HBs antibody concentration decreasing to 100 IU/L or lower (even after dosage adaptation), patients were to be withdrawn from further participation in this study.

After week 4 posttransplantation, administration of HBIG could be undertaken by the patient or a caregiver after assessment in the transplant unit if they complied with the subcutaneous injection technique after a training program, and if anti-HBs trough level was greater than 100 IU/L. Compliance with the HBIG dosing regimen was monitored by documentation in a patient diary that was checked at each study visit and confirmed by measurement of anti-HBs titers.

Concomitant antiviral therapy with a nucleoside/nucleotide analogue was administered to all patients according to local practice.

**Data Collection and Analysis**

Serum HBs antibodies concentrations were determined before HBIG administration once a week for the first 4 weeks, once every week or 2 weeks (at the discretion of the investigator) to week 9, then once every 4 weeks. Recurrence of HBV infection of the transplanted liver (based on HBsAg positivity and clinical symptoms), laboratory data, and the occurrence of adverse events were documented throughout the 6-month study.

Patient diaries were used to record compliance with home administration of subcutaneous HBIG. Additionally, the diaries...
were used for patients to record their responses to the following questions: “Was taking HB Ig by subcutaneous injection convenient for you?” “In your opinion, is the subcutaneous application easy to handle?” “Overall, were you satisfied with your HB Ig treatment?”

The primary endpoint of the study was failure rate by month 6, defined as serum anti-HBs of 100 IU/L or less or HBV reinfection (ie, HBsAg positivity and clinical symptoms) despite serum anti-HBs greater than 100 IU/L. The sample size calculation estimated that a population of 40 evaluable patients would provide 84% power to observe a 3.5% failure rate with a 2-sided 95% confidence interval (CI) of 16.3% (0.6-16.9) based on the assumption that the failure rate would not exceed 5%. The literature indicates that intravenous or intramuscular administration of HB Ig can effectively maintain anti-HBs levels above 100 IU/L and that combination therapy with antiviral agents reduces the reinfection rate to less than 10%.9,11,17,27

For the primary endpoint, a 2-sided 95% CI was calculated using the Clopper-Pearson method. All other variables were analyzed descriptively, with 95% CI values where appropriate. In the event of missing efficacy data, the last observation carried forward principle was applied.

The safety population comprised all patients who received at least 1 dose of subcutaneous HB Ig. The intention-to-treat population comprised all patients who received at least 1 dose of subcutaneous HB Ig and provided at least 1 postdose efficacy assessment. All patients met the criteria for inclusion in both populations.

All statistical analyses were performed using SAS software (Version 8.2 or higher).

RESULTS

Patient Population

In total, 75 patients were recruited, of whom 19 were excluded before the screening visit because an adequate number of evaluable patients had already entered the study (Figure 1). Seven patients did not meet the eligibility criteria at screening, such that the study population comprised 49 patients, all of whom were treated with subcutaneous HB Ig (Table 1). Two patients discontinued the study prematurely: 1 was lost to follow-up and 1 discontinued due to graft rejection.

The majority of patients were men (41/49, 83.7%) and white (45/49, 91.8%). Forty-five patients were transplanted due to HBV-induced cirrhosis (91.8%), with hepatocellular carcinoma listed as a cause of transplantation in 24 cases (49.0%). Twenty-one patients (42.9%) were coinfected with hepatitis D. Five patients (10.2%) experienced graft rejection during the study.

Before the informed consent, 39 patients were HBV DNA-negative. Hepatitis B virus DNA was undetectable in 48 patients both at the point of informed consent signature and time of liver transplant, as per the inclusion criteria (information was missing in 1 patient). As per protocol, all 49 patients were HBsAg-negative at the time of the first dose of subcutaneous HB Ig. All donors were HBsAg-negative. Forty patients (81.6%) were receiving antiviral therapy before transplantation.

HBIg Therapy and Concomitant Medication

Subcutaneous HB Ig was started during days 8 to 11 posttransplantation in 37 patients and during days 15 to 18 in the remaining 12 patients. At study entry, a weekly treatment schedule was documented in 20 patients. The other 29 patients received treatment every 2 weeks. The initial subcutaneous dose was 500 IU in 19 of the 20 patients dosed weekly, and in 22 of the 29 patients treated once every 2 weeks. By the final visit, the proportion of patients requiring a dose of 1000 IU had increased slightly in both the weekly and biweekly dosing groups (Table 2). In total, 13 doses of 1500 IU were administered in 5 patients during the study.

Subcutaneous HB Ig could be injected at home by the patient or a caregiver (eg, family member or other nonprofessional care worker) after week 4 posttransplantation. All patients achieved administration by a caregiver or self-injection by week 14 and continued until the end of the study (except for 1 patient at 2 study visits). All patients received concomitant antiviral therapy, comprising entecavir (n = 27), lamivudine (n = 12), tenofovir (n = 10), and adefovir (n = 1).

The immunosuppression regimen included tacrolimus in all except 1 patient. Other maintenance immunosuppressants comprised mycophenolate mofetil (n = 29), everolimus (n = 16), sirolimus (n = 2) and cyclosporine (n = 2 [including

<table>
<thead>
<tr>
<th>TABLE 1. Baseline characteristics (n = 49)</th>
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<tbody>
<tr>
<td>Age: mean (SD), y</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
</tr>
<tr>
<td>White, n (%)</td>
</tr>
<tr>
<td>Indication for liver transplantation, n (%)a</td>
</tr>
<tr>
<td>HBV-induced cirrhosis</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Acute liver failure</td>
</tr>
<tr>
<td>Retransplantation</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Coinfection with hepatitis D virus, n (%)</td>
</tr>
<tr>
<td>Antiviral therapy pretransplant, n (%)</td>
</tr>
<tr>
<td>HBV-DNA negative at time of transplant, n (%)</td>
</tr>
</tbody>
</table>

a More than 1 reason could be selected.
TABLE 2.
Subcutaneous HB Ig administration (n = 49)

<table>
<thead>
<tr>
<th>Dosing interval</th>
<th>IU</th>
<th>1510</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once a week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>19</td>
<td>(38.8)</td>
</tr>
<tr>
<td>1000</td>
<td>1</td>
<td>(2.0)</td>
</tr>
<tr>
<td>Once every 2 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>22</td>
<td>(44.9)</td>
</tr>
<tr>
<td>1000</td>
<td>5</td>
<td>(10.2)</td>
</tr>
<tr>
<td>1500</td>
<td>2</td>
<td>(4.1)</td>
</tr>
<tr>
<td>Final dose, IU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once a week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>15</td>
<td>(30.6)</td>
</tr>
<tr>
<td>1000</td>
<td>5</td>
<td>(10.2)</td>
</tr>
<tr>
<td>Once every 2 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>20</td>
<td>(40.8)</td>
</tr>
<tr>
<td>1000</td>
<td>8</td>
<td>(16.3)</td>
</tr>
<tr>
<td>1500</td>
<td>1</td>
<td>(2.0)</td>
</tr>
</tbody>
</table>

1 patient converted from tacrolimus), with corticosteroids in 40 patients.

Efficacy

All patients maintained serum HBs antibody concentrations greater than 100 IU/L and remained HBsAg-negative throughout the 6-month study. Thus, no treatment failures occurred (0.0 [95% CI, 0.0-0.0725]).

Figure 2 illustrates the course of anti-HBs levels during the study. Mean (SD) anti-HBs was 1095 (527) IU/L before the first dose of subcutaneous HB Ig, and 292 (147) IU/L at the end of the 6-month study. Mean anti-HBs peaked at the time of the second subcutaneous dose (mean [SD] 1112 [776] IU/L), then declined progressively to month 6, plateauing at approximately 290 IU/L. After the first dose of subcutaneous HB Ig, the minimum anti-HBs level observed in any patient at any time point was 115 IU/L (Figure 2). Maximum values ranged from 5017 (after the first dose) to 1000 IU/L (from week 8 onward).

One patient experienced transient splenomegaly, which was present before the first dose of subcutaneous HB Ig on day 7. No clinical symptoms consistent with HBV reinfec-
tion were observed during the study.

Mean (SD) values for alanine transaminase, aspartate aminotransferase, γ-glutamyltransferase, alkaline phosphatase and total bilirubin at the final study visit were 30.5 (22.4) IU/L, 25.5 (11.1) IU/L, 49.7 (52.9) IU/L, 105.7 (49.4) IU/L, and 0.61 (0.3) mg/dL, respectively. No liver function test showed a clinically relevant abnormality in more than 2 patients at the final visit.

Safety and Tolerability

Forty-five patients reported 1 or more adverse event during the study, 1 of which (graft rejection) led to study discontinuation but was not considered related to study treatment. No adverse event resulted in a change to the HB Ig dose. Only 1 adverse event, a mild injection site hematoma, was assessed as treatment-related, and HB Ig administration was not altered as a consequence. No serious drug-related adverse events occurred.

No patient showed clinically abnormal levels of IgG, IgA, or IgM at the final study visit.

Patient Attitudes

All patients responded “yes” to the question “Overall, were you satisfied with your HB Ig treatment?” at all study visits. The handling of the subcutaneous application was assessed to be easy (yes/no response) by 92% of patients by week 4, increasing to 100% from week 16 onward. Furthermore, patient diaries indicated 100% compliance throughout the study.

DISCUSSION

This is the first study to investigate the efficacy of starting subcutaneous HB Ig for HBV reinfection prophylaxis, dosed according to serum anti-HBs trough level, by week 3 after
In this cohort of 49 patients receiving concomitant antiviral therapy, all of whom were HBV DNA-negative at time of transplant, early switch to weekly or fortnightly subcutaneous administration maintained serum anti-HBs at a level that effectively prevented HBV reinfection in all patients. After switch to subcutaneous HBIg, no patient had an anti-HBs level below 100 IU/L. Most patients were maintained on a subcutaneous dose of 500 IU once a week (~30%) or once every 2 weeks (~40%). There were no cases of HBV recurrence and no laboratory or pathological signs characteristic of HBV reactivation of the graft during the 6-month trial other than 1 case of splenomegaly which was present before the first dose of HBIg.

The study did not seek to determine the effectiveness of HBIg therapy per se, and thus did not include an HBIg-free control arm. Instead, the aim was to examine outcomes with very early switch to the subcutaneous route of administration, instead of extended intravenous therapy or use of intramuscular injection. The subcutaneous route facilitates administration of HBIg at home, an approach that is convenient for patients and reduces staff time. A trial comparing intramuscular to subcutaneous HBIg injection reported that patients found subcutaneous administration to be less painful and preferred it to the intramuscular route.\textsuperscript{1,7} Typically, conversion from intravenous to subcutaneous administration has been carried out no earlier than 6 months after liver transplantation.\textsuperscript{18,19,23} In 1 small pilot study, 12 de novo liver transplant patients (all of whom were HBV DNA-negative and HBsAg-positive before transplantation) were converted at a median of 25 days’ posttransplantation from intravenous HBIg (30 000 IU) to subcutaneous therapy.\textsuperscript{24} The subcutaneous dose was 500 or 1000 IU per week, according to body weight.\textsuperscript{24} In that series, the anti-HBs titers remained at 150 IU/L or above throughout 6 months of follow-up, with no viral breakthrough. These results are consistent with our own findings in which switch to subcutaneous therapy took place even earlier.

The dosage regimen for HBIg is currently a matter of controversy, particularly in relation to proposals that low-dose treatment should be started during the anhepatic phase.\textsuperscript{1,4} In the current study, the subcutaneous dosage regimen was flexible, within protocol-defined limitations: 500 to 1000 IU was selected according to anti-HBs trough levels, with the starting dose also depending on the HBsAg and anti-HBsAb status achieved within the first week posttransplantation during intravenous HBIg administration. This individualized approach is consistent with the product license for marketed intravenous HBIg preparations, which states that patients 1 week after liver transplantation should receive doses of HBIg as high as necessary to maintain antibody levels above 100 to 150 IU/L in HBV-DNA-negative patients. There was a clear trend in our population for the anti-HBs levels reached throughout and after the intravenous dosing phase to be lower than anticipated based on the pharmacokinetic characteristics of intravenous HBIg. This was duly accounted for by the investigators through frequent uptitration of the subcutaneous dose when the serum anti-HBs levels were lower or declined faster than might have been expected. In general, such increases achieved higher anti-HBs levels. In the absence of a protocol-specified dosing algorithm, the subcutaneous dose need not be increased if the anti-HBs titer is close to 100 IU/L, avoiding the potential overtreatment in some patients that could occur with a fixed treatment regimen. This, additionally, could be expected to yield potential cost savings.

Previous studies have demonstrated that home administration of subcutaneous HBIg is effective.\textsuperscript{18,19,23} A single-arm 18-week trial undertaken in 23 liver transplant patients has shown that conversion from monthly intravenous HBIg to self-administered weekly subcutaneous therapy maintained trough anti-HBs concentrations above 100 IU/L in all cases.\textsuperscript{18} In that series, all patients were a minimum of 3 months posttransplantation at the time of conversion. A larger study (n = 135), in which all patients were at least 12 months posttransplantation, confirmed that anti-HBs concentration consistently remained above 100 IU/L using self-administered weekly subcutaneous HBIg throughout a 48-week monitoring period.\textsuperscript{19} More recently, an observational study in 61 patients, who were converted to subcutaneous HBIg at a median of 5.7 months posttransplantation and self-administered at home, found an anti-HBs serum concentration below 100 IU/L at 1 or more points in 4 patients.\textsuperscript{23} In each case, however, HBIg treatment had been interrupted by the investigator in response to declining anti-HBs levels, and lack of efficacy or noncompliance was not the cause of low anti-HBs levels. In our study, there was full compliance with the prescribed once weekly or once fortnightly regimen and the serum HBs antibody concentration was above 100 IU/L throughout the study in all patients. In addition, it has been shown in liver transplant patients receiving combination prophylaxis with HBIg plus a nucleos(t)ide inhibitor that a serum anti-HBs level of 50 to 100 IU/L is protective in the medium term.\textsuperscript{14} This suggests that outside clinical trials, this target level of anti-HBs after the first few months posttransplantation could be sufficient for effective prophylaxis.

Subcutaneous HBIg was well tolerated. The only adverse event related to subcutaneous HBIg was a mild infection site hematoma. No patient discontinued study drug due to treatment-related adverse events, consistent with previous reports.\textsuperscript{18,23} The regimen was well accepted by patients: all participants who commented at the end of the 6-month study found subcutaneous administration to be convenient.

The findings from this prospective, multicenter study indicate that introduction of subcutaneous HBIg administration by week 3 after liver transplantation, dosed according to serum anti-HBs trough level and combined with HBV virostatic therapy, is an effective, safe and convenient strategy for preventing HBV recurrence after liver transplantation.

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REFERENCES


