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Brief Clinical Observation

Extended HBV vaccination in liver transplant recipients for HBV-related cirrhosis: Report of two successful cases

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Abstract

The effectiveness of hepatitis B virus vaccination in liver transplant recipients for hepatitis B virus-related end-stage liver disease is controversial. We report two successful cases, who developed sustained protection after long-term vaccination. Case 1. A 58-year-old male, transplanted 9 years earlier, received three intramuscular monthly doses of 40 μg of recombinant S vaccine and developed an anti-hepatitis B surface titre of 154 IU/L. After an additional 40 μg dose, he reached an anti-hepatitis B surface peak of 687 IU/L and then maintained a "protective" titre (>100 IU/L) without further vaccinations for the next 40 months. At this time, revaccination with three monthly doses of 40 μg resulted in an anti-hepatitis B surface titre greater than 25,000 IU/L, sustained over time. Case 2. A 56-year-old woman, transplanted 8 years earlier, first received three intramuscular monthly doses of 40 μg of S vaccine without developing any detectable anti-HBs. She was then given multiple intradermal vaccine doses which resulted in a titre of 37 IU/L. Next, after readministration of three 40 μg intramuscular monthly doses, she developed an anti-HBs titre of 280 IU/L. In the following 4 years, the anti-HBs titre dropped below 100 IU/L four times (at month 20, 30, 38 and 44) and readministration of single 40 μg doses of vaccine was always sufficient to restore a protective titre.

Conclusion. Extended HBV vaccination may afford valid protection against HBV recurrence in selected liver transplant recipients.

Keywords: Anti-HBs titre; HBV vaccination; Hepatitis B immunoglobulins

1. Introduction

Hepatitis B virus (HBV) reinfection after orthotopic liver transplantation (OLT) for HBV-related cirrhosis occurs in more than 70% of the cases in the absence of immunoprophylaxis and is associated with poor prognosis due to the rapid development of cirrhosis, fibrosing or fulminant hepatitis [1,2]. The introduction in the early 90s of anti-HBs immunoglobulins (HBIg) as a prevention strategy of HBV reinfection significantly reduced the rate of graft reinfection, allowing OLT for HBV-related end-stage liver disease to be performed with a great improvement in patient survival [3–5]. Nowadays, more than 10 years later, HBIg immunoprophylaxis is still considered the mainstone to prevent HBV reinfection. According to the current concepts, HBIg should be administered indefinitely in all patients who were HBsAg positive prior to the transplant [6], as HBV-DNA persistence has been observed even 10 years after liver transplantation despite successful passive immunoprophylaxis [7]. Yet, HBIg administration is associated with a number of problems: first, HBV recurrence is observed in a non-negligible (up to 15–30%) number of cases when HBIg are used as monotherapy [6], possibly due to the emergence of HBV envelope protein mutations [8,9], or to suboptimal HBIg administration, the latter being favoured by the remarkable inter- and intra-individual HBIg consumption variability [10]; second, the minimum through levels of anti-HBs to be maintained during the different periods after OLT is a matter of debate, and there is also uncertainty with

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regard to the optimal mode of administration and the duration of the prophylaxis (most centres administer HBIg on a life-long basis). Third, HBIg are extremely costly and often even of limited availability and the need of long-term administration has a negative impact on the patients' quality of life. Recently, the introduction of lamivudine used in combination with HBIg has enhanced the protection level given by HBIg monoprophylaxis [11–14]; in addition, the use of personalised schedules (given "on demand") allows to reduce the total amount of HBIg to be given and the number of administrations [10], thus contributing to the cost reduction and improved quality of life. Currently, the recommended prophylactic treatment against HBV infection recurrence after OLT is the combination of low doses of HBIg and lamivudine [14,15], yet there is a clear need for alternative strategies. The availability of an effective HBV vaccination would be ideal in this setting. Unfortunately, HBV vaccination is poorly effective in immunocompromised patients [16,17], including those receiving immunosuppressive drugs after liver [18] or kidney [19] transplantation and in patients with hepatitis C [20] or cirrhosis [21,22]. The use of reinforced or accelerated vaccination schedules has been shown to increase the immunogenicity of the conventional recombinant S vaccine, conferring improved protection in some categories of poor responders to the standard schedule [23]. Yet, in OLT recipients, due to HBV-related liver disease, this approach has given contradictory results [25,28]. Moreover, the interpretation of the results is confused by the lack of definition of the minimum anti-HBs "protective" titre in this setting and by the differences in patient population between the published studies [24]. In a previous study by our group [25], 17 patients transplanted due to HBV-related cirrhosis received a reinforced schedule of recombinant S vaccine, which was administered both through the intramuscular and the intradermal route. The intradermal route was adopted because of the reported greater efficacy versus the intramuscular route in non-responsive chronic dialysis patients [26,27]. Despite this approach, only two patients in our study mounted a significantly "protective" anti-HBs titre, which lasted for at least a few months. In the present paper, we report the long-term follow-up (more than 4 years) of these two responders, including details on the further vaccine doses needed to maintain high anti-HBs titres and to avoid continuation of HBIg immunoprophylaxis.

1.1. Case 1

A 58-year-old (R.I.) white man had undergone OLT due to HBV cirrhosis 9 years earlier. The patient was negative for HBV DNA by hybridisation assay and for HBeAg at time of transplant. He had been given 2.5 mg/kg of cyclosporine A microemulsion (CyA) as immunosuppressive monotherapy and had received HBIg immunoprophylaxis (5000 IU intravenously, monthly) since transplantation. Four years after OLT, the patient was started on lamivudine (100 mg/day) and HBIg administration was interrupted. The vaccination program was begun 16 weeks after the last HBIg administration, when the anti-HBs titre had dropped to less than 10 IU/L. The patient received a first vaccination cycle consisting of three intramuscular monthly doses of 40 μg of recombinant S vaccine (Recombivax HB, Pasteur Meriéux/MD, Lyon, France). Anti-HBs titres were measured monthly during the whole study period using a third-generation immunoenzymatic assay (AUSAB EIA, Abbot, Baar, Switzerland). One month after the third vaccine dose, the anti-HBs titre rose to 154 IU/L. The patient received an additional dose of 40 μg of vaccine at month 6, developing 1 month later an anti-HBs titre of 687 IU/L. The titre then remained within the "protective" range (defined here as >100 IU/L) for the next 27 months with a median level of 1712 IU/L (range 265–9000 IU/L). Then spontaneously rose to more than 25,000 IU/L, remaining around this level for the next 11 months. Beginning from month 44 after the first vaccine dose, the anti-HBs titre progressively decreased, finally reaching a "non-protective" titre (27 IU/L) within a further 6-month period. During the entire period in which the anti-HBs titre was above the "protective" threshold, the patient interrupted any antiviral or HBIg treatment, nor did he receive additional doses of vaccine. A new vaccination cycle identical to the initial schedule (three doses of 40 μg at monthly intervals) was administered beginning from month 48. This was followed by a rapid and strong response (>25,000 IU/L) lasting until present. The total dose of recombinant S vaccine so far received by this patient amounted to 280 μg, with a corresponding cost of €630 significantly less compared to the €38,000 per year of the HBIg prophylaxis received prior to vaccination (in Italy 5000 IU of HBIg cost €3170). The patient experienced no side effects during the entire vaccination period and remained always HBsAg negative. Quantitative HBV-DNA determinations, performed by Roche Monitor Amplicor PCR assay prior to vaccination, and then yearly were constantly less than 400 copies/ml. The changes in anti-HBs titre during the whole observation period of 57 months are depicted in Fig. 1, and the vaccination schedule is summarised in Table 1. Lamivudine was withdrawn at month 6, when the anti-HBs titre became consistently above 500 IU/L and not reassumed until now.

1.2. Case 2

A 56-year-old woman (A.D.) who had undergone OLT due to HBV-related cirrhosis 8 years earlier. The patient was anti-HDV positive and was HBV-DNA negative by hybridisation assay as well as HBeAg negative. She had been given 1.8 mg/kg of CyA monotherapy as the only immunosuppressive treatment and had received HBIg immunoprophylaxis (5000 IU intravenously, monthly) since transplantation. Three years after OLT the patient was started on lamivudine (100 mg/day) and HBIg administration was interrupted. The vaccination program was begun 14 weeks after the last HBIg administration, when the anti-HBs titre was <10 IU/L. As in the previous case, the patient received a first vaccination