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LETTER TO THE EDITORS

Chronic rejection related to hepatitis B immunoglobulin discontinuation in a liver transplant recipient

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Dear sirs,

Combination hepatitis B immunoglobulin (HBIG) and antiviral therapy is highly successful in preventing recurrence of hepatitis B virus (HBV) after liver transplantation (LT) [1]. Given the cost and inconvenience of HBIG treatments, there has been recent interest in discontinuing HBIG in favor of oral antivirals with low associated resistance. Studies have shown that this practice is safe with minimal risk of HBV recurrence [2]. However, as HBIG is an immunological agent similar to intravenous immunoglobulin (IVIG), there may be a theoretical risk of immune activation after stopping HBIG. We present a case of a LT recipient who developed chronic rejection shortly after HBIG discontinuation with resolution once HBIG was reinstituted.

The patient is a 59-year-old Asian male who received an orthotopic LT in August 1997 for hepatitis B cirrhosis. His HBV prophylaxis consisted of lamivudine 100 mg daily and 1000 international units (IU) of HBIG intramuscular injections monthly since transplantation. He was on tacrolimus monotherapy since early transplantation. He was monitored with monthly laboratory tests, tacrolimus trough levels, and hepatitis B surface antibody titers that were consistently maintained at >100 IU/l. He had no history of HBV recurrence or allograft rejection and had normal liver function tests for over 10 years. In May 2006, a liver biopsy was performed and was normal. Due to the cost and inconvenience of HBIG injections, HBIG was discontinued on March 20, 2008. HBV DNA and surface antigen were undetectable at that time. Adefovir 10 mg daily was added to lamivudine for HBV prophylaxis.

On May 22, routine laboratory tests showed rising aminotransferase levels (Graph 1). On June 9, the total bilirubin was 1.6 mg/dl, aspartate aminotransferase (AST), 302 U/l; alanine aminotransferase (ALT), 503 U/l; and alkaline phosphatase (AP), 360 U/l. The tacrolimus trough level was 7.6 and there was no evidence of hepatitis B recurrence (HBV DNA undetectable, Hepatitis B surface antigen negative). A liver biopsy revealed only three out of ten portal triads with bile ducts and bridging fibrosis, which suggested chronic rejection. Due to recent discontinuation of HBIG, he was restarted on HBIG intravenously (10 000 IU) on June 13. The aminotransferase levels trended down within 1 week (Graph 1). With no additional immunosuppressive agents, on June 23 the AST was 25 U/l; ALT 53 U/l; and AP 195 U/l.

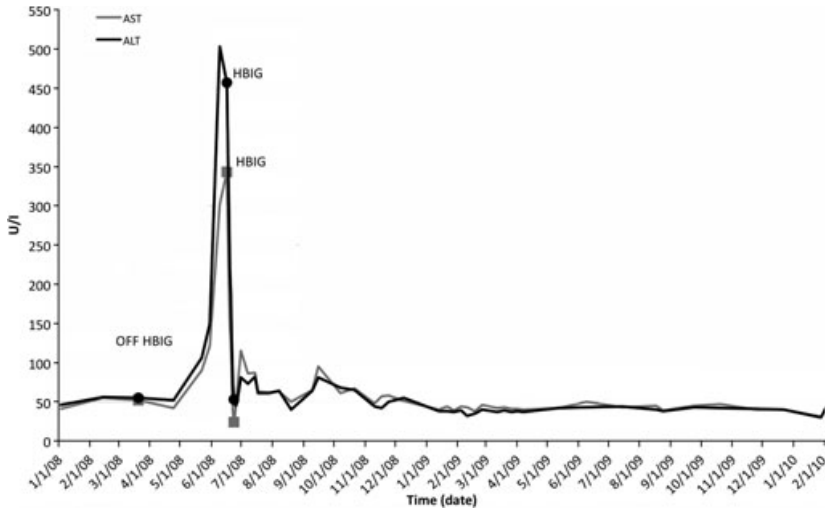
A repeat liver biopsy in August 2009, 14 months after HBIG was restarted, revealed complete resolution of chronic rejection. He continues to receive monthly HBIG therapy and his laboratory values have remained stable.

Discussion

Since the 1990s, the emergence of HBV prophylaxis has made a tremendous impact on the survival of HBV + LT recipients. HBIG alone has decreased the risk of HBV recurrence from 75% to 36% and combined with lamivudine it has further decreased to 0–10% [1,3]. HBIG provides immediate passive protection while antivirals reduce viral replication and prevent saturation of HBIG binding sites [1]. The disadvantages of long-term HBIG include high cost, inconvenient administration, and decreased effectiveness alone in patients with higher viral loads [2]. Recent studies have demonstrated low HBV recurrence with HBIG discontinuation and eventual lamivudine monotherapy [2]. Antivirals with better resistance profiles (tenofovir, entecavir) appear promising for long-term HBV prophylaxis [2].

These studies have not described a direct immunological benefit of HBIG or reported any cases of graft rejection on HBIG discontinuation as seen in this report. This may indicate that these occurrences are either under reported, under recognized or extremely rare. The mechanism is unknown, but nonspecific IVIG has inhibitory effects on dendritic cell presentation and T cell proliferation [4]. Denys *et al.* highlighted another immunosuppressive mechanism of both IVIG and HBIG via interferon-γ antibodies [5]. Clinically, Couto *et al.* reported that use of long-term HBIG therapy was associated with less rejection episodes in LT recipients [6].

Chronic allograft rejection in this case was likely precipitated by the discontinuation of HBIG. The timing of



Graph 1 Aminotransferase levels in relation to HBIG therapy. Note abrupt increase in AST (aspartate aminotransferase) and ALT (alanine aminotransferase) with discontinuation of HBIG and dramatic decrease of those levels once HBIG was given. These levels have remained stable with reinstitution of monthly HBIG treatments.

HBIG discontinuation to increased liver enzymes and biopsy-proven chronic rejection with immediate improvement with HBIG reinstitution strongly suggests this was HBIG-related. Prior ongoing low-grade chronic rejection is possible. We do not perform protocol biopsies and therefore cannot exclude a pre-existing immunological process, although his liver enzymes and biopsy (2006) were normal prior to HBIG discontinuation. Sampling variation between the biopsies could have also occurred. However, the improvement in three stages of fibrosis with biopsies of adequate sample size (>2 cm) minimizes the possibility of sampling error [7].

Chronic rejection has been generally believed to evolve over months to years and to be irreversible. Though chronic rejection in this case appears to have occurred over a relatively short time, 3 months after HBIG discontinuation and resolution within 14 months on biopsy, the Banff group has reported that chronic rejection can range from rapid development to months to years [8]. Also histological changes of chronic rejection (bile duct loss, central fibrosis) can be reversible [9]. Demetris *et al.* showed biochemical and histological improvement in chronic rejection after conversion from cyclosporine to tacrolimus. An initial total bilirubin <20 mg/dl and <50% duct loss on biopsy were predictors of a good response [10]. The recovery of bile ducts was seen 100–400 days after the initial biopsy. Our patient's initial biopsy had more than 50% duct loss, but his bilirubin was 6 mg/dl supporting the potential for reversibility.

Given these immunosuppressive properties of HBIG and the implications of this case, an increased awareness of rejection and immunological complications should be taken into consideration when deciding to discontinue HBIG therapy. The incidence of rejection is still likely low and there may have been other unknown influences or pre-existing abnormalities precipitating rejection in this case. Transitioning to only antiviral therapy may still be a safe option for most patients. However, more frequent laboratory testing (we recommend every 2 weeks for 3 months and then monthly after HBIG discontinuation) and maintenance of other immunosuppression levels should be utilized to monitor for both HBV recurrence and graft rejection. Further investigational studies are needed to clarify the immunological properties of HBIG and the incidence, risk factors, and mechanism of rejection with HBIG withdrawal.

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Conflict of interest and funding statement

There is no funding or conflict of interest to declare.

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