

Case reports

Horse antilymphocytic globulin in hepatitis B exacerbation after bone marrow transplantation adoptive immunity transfer

C Favre¹, MC Menconi¹, M Nardi¹, G Casazza¹, F Oliveri², P Macchia¹, F Bonino² and MR Brunetto²

¹Unità Trapianto di Midollo, Clinica Pediatrica I, Italy; and ²UO Gastroenterologia ed Epatologia, Azienda Ospedaliera-Universitaria Pisana, Pisa, Italy

Summary:

We describe the case of a HBsAg+, HBeAg+ carrier, treated with lamivudine, who experienced exacerbation of hepatitis after BMT from an anti-HBs+, anti-HBc+, anti-HBe+ donor. The serological profile of the donor and the timing of exacerbation suggested that the adoptive immunity transfer played a major pathogenetic role. Antilymphocyte globulin administration resulted in resolution of hepatitis and seroconversion to anti-HBs+. Therapy aimed at blocking the effector arm of liver damage could represent a novel approach to avoid the risk of progression to fulminant hepatitis without hampering the chances of recovery from hepatitis B.

Bone Marrow Transplantation (2004) 33, 1057–1059
doi:10.1038/sj.bmt.1704471

Published online 29 March 2004

Keywords: hepatitis B; antilymphocytic globulin

Chronic or *de novo* acquired Hepatitis B virus (HBV) infection cause significant morbidity and mortality after bone marrow transplantation (BMT). Previous reports showed that the incidence of hepatitis is significantly higher in HBsAg-positive as compared to HBsAg-negative recipients.¹ The major cause of such cases is HBV reactivation,² that may result in hepatic failure or death. On the basis of these observations and the availability of antiviral drugs, in the last years the treatment of HBsAg carriers with nucleoside analogs before and after BMT has been proposed.³ Preliminary reports suggest that antiviral therapy may reduce the incidence of post-BMT HBV reactivation and hepatitis. Nevertheless, some patients still develop HBV-related complications.³ Therefore, antiviral treatment should be optimized and alternative therapeutic strategies explored if hepatitis B reactivates.⁴ The role of the adoptive transfer of specific anti-HBV immunity into a HBV carrier via a HBV-immune donor should also be studied in terms of HBV clearance and risk of hepatitis B exacerbation.⁵

Case report

In May 1999, a 5-year-old girl with acute lymphoblastic leukemia (ALL) in second complete remission (CR) was referred from Venezuela to our institution for allogeneic bone marrow transplant (BMT) from her 7-year-old human leukocyte antigen (HLA)-identical brother.

The patient was a chronic HBV carrier (HBsAg+, HBeAg+), and had detectable levels of HBV-DNA (1×10^6 copies/ml, detected by Monitor HBV, Roche, UK). She was IgM anti-HBc+ [IMx Index 0.44 (by Core-M assay, Abbott Laboratories, North Chicago, IL, USA) using 0.200 IMx Index as chronic hepatitis cut-off and 0.100–0.200 IMx Index values as 'chronic hepatitis gray zone'.⁶ ALT was 50 U/l. Her brother was anti-HBs+ (3900 IU/ml), anti-HBc+, and anti-HBe+, had no detectable HBV-DNA and had normal liver enzyme (AST 27 U/l, ALT 31 U/l). The patient started antiviral therapy with lamivudine (75 mg/day) and maintenance chemotherapy (6-mercaptopurine, methotrexate, and intrathecal Ara-C + methotrexate + steroids). During treatment, HBV-DNA and IgM anti-HBc levels progressively decreased, HBV-DNA levels fell below the sensitivity limits of the assay (<400 copies/ml) after 6 months, and IgM anti-HBc reduced to 0.22 IMX Index. Transaminases were normal and HBsAg and HBeAg remained detectable.

She was allografted after 6 months of lamivudine after cyclophosphamide 120 mg/kg; thiotepa 10 mg/kg, and TBI 12 Gy (in six fractions) followed by i.v. infusion of unmanipulated bone marrow (5.9×10^8 mononuclear cells/kg) from her brother. Cyclosporine was used to prevent graft-versus-host disease (GVHD), and fluconazole, ciprofloxacin, acyclovir, and lamivudine administered prophylactically.

Fever developed on day 13 with elevation of transaminases (AST 104 U/l and ALT 110 U/l); Alkaline phosphatase, bilirubin, and prothrombin time were normal. Liver and spleen were not enlarged. The patient showed some signs of engraftment on day 15, when HBV-DNA (4000 copies/ml) and IgM anti-HBc (Imx Index 1.3) were detectable. On day 16, liver enzymes were significantly increased (AST 1574 U/l; ALT 1568 U/l); with bilirubin 1.7 mg/dl, PT 52% (normal 70–100%), INR 1.57 (normal 0.9–1.15), and PTT 50 s (normal 25–40 s). Liver was palpable 4 cm beneath the costal margin. HBV-DNA level reached 8000 copies/ml.

Correspondence: Dr C Favre, BMT Unit, Department of Pediatrics, Via Roma 67, 56126 Pisa, Italy. E-mail: c.favre@med.unipi.it
Received 22 March 2003; accepted 12 December 2003; published online 29 March 2004

No clinical manifestations of GVDH or VOD were seen. CMV antigenemia was negative and blood cyclosporine level was within the normal range. Ganciclovir (10 mg/kg/day) was added as antiviral therapy, and horse ALG (SangStat Medical Corporation, 1.5 vials/10 kg/day × 5 days, then on alternate days up to day 29) and Mycophenolate (250 mg/day until day 58) were administered as immunosuppressive therapy.

From day 17 transaminases levels decreased progressively, reaching normal values on day 44. On day 27, the liver became impalpable. On day 30, HBV-DNA was <400 copies/ml and IgM anti-HBc was 2.6 IMX values; their levels decreased thereafter (on day 60: IgM anti-HBc 1.2 IMX values; on day 90: IgM anti-HBc 0.8 IMX values) and on day 90 anti-HBe antibodies were detectable (Figure 1). At 10 months post-BMT, transaminases were within the normal range, and HBsAg was negative and anti-HBs was positive. Full engraftment was seen on day 28.

Discussion

Our patient, despite significant inhibition of a chronic HBV infection with lamivudine, experienced severe hepatitis B exacerbation 15 days after BMT from an anti-HBs, anti-HBc, anti-HBe positive donor. The severity of the hepatitis flare was controlled by immunosuppressive therapy specifically targeted to block activated lymphocytes (ALG).

Severe hepatitis B exacerbations may be life-threatening in HBV carriers undergoing BMT. Usually, hepatitis flares

are observed a few months after BMT during tapering of immunosuppressive drugs, and are preceded by a significant increase of HBV-DNA levels (and reappearance of serum HBeAg in anti-HBe carriers). These events suggest that HBV reactivation, induced by immunosuppressive therapy, plays a major role in the hepatitis B exacerbation. In our patient, the hepatitis flare occurred early and without a significant increase in serum HBV-DNA.

Marked elevation of liver enzymes early after BMT is rare. A review from the Seattle group reported a severe hepatocellular injury in 1.8% of cases within first 100 days after transplant.⁷ No case of HBV hepatitis was observed. The main cause of marked AST elevation early after BMT (day 23 ± 9) was VOD. Our patients did not have any clinical evidence of VOD. The other two possible etiologies, varicella zoster (VZV) hepatitis and ischemic hepatopathy, were not consistent with the clinical and biochemical profile of our patient. Also, the patient was on acyclovir which would have prevented VZV reactivation. Ischemic hepatopathy usually occurs with sepsis, cardiogenic shock, or multiorgan failure, all absent in our patient.

The increase of anti-HBc IgM (from 0.22 IMX index at baseline to 1.3 IMX index at the time of the ALT flare) supports the diagnosis of HBV-induced liver damage. An early HBV reactivation or selection of a YMDD mutant were excluded by the slight increase of HBV-DNA levels and by direct sequence of serum sample obtained on day 15. The serological profile of the donor suggesting recent exposure to HBV (with possible exposure to the same HBV strain, via household contact), and the coincidence of the ALT flare with the recovery of bone marrow function

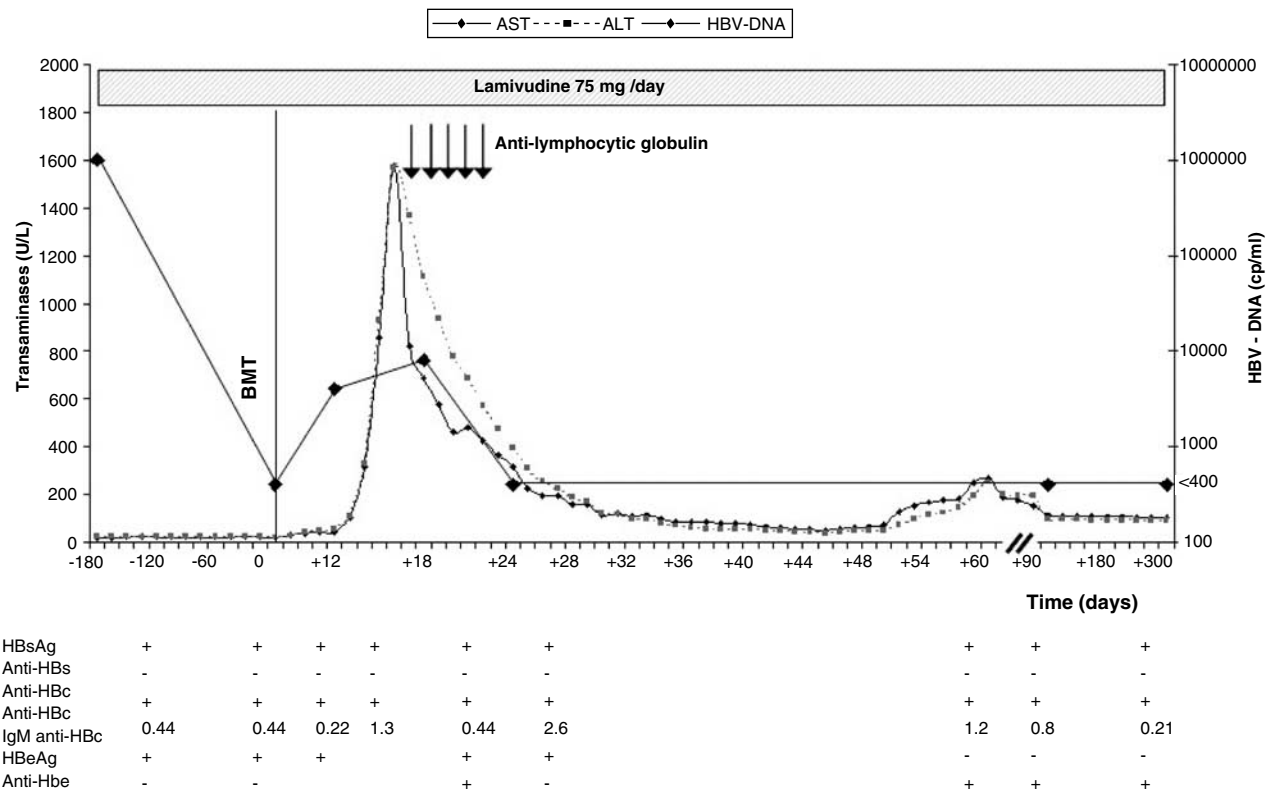


Figure 1 Biochemical and HBV markers profile during the hepatitis exacerbation.

suggests that the adoptive immunity transfer possibly played a role in the exacerbation of hepatitis.

Our patient had ongoing HBV replication and serum HBeAg at the time of BMT. A florid expression of viral antigens at the hepatocyte level could have favoured a rapid recruitment of activated lymphocytes within the liver at the time of bone marrow recovery. The sudden liver enlargement, brisk ALT elevation, and deranged coagulation suggested a high risk of severe progression of liver damage prompting a strong immunosuppressive therapy. Rapid improvement of both clinical and biochemical parameters was seen after ALG was started. Clearance of serum HBV-DNA with HBeAg to anti-HBe and HBsAg to anti-HBs seroconversion suggests that the inhibition of T-cell activity did not abrogate the effectiveness of the immune control of HBV infection. The evidence that ALG were able to block the progression of liver damage without compromising both the recovery from hepatitis B and the seroconversion to anti-HBs is in accordance with studies in animal models and preliminary reports in humans suggesting that non-specific T-cell recruitment plays a major role in the pathogenesis of liver damage.⁸⁻⁹ Recently, Guidotti *et al*⁸ showed in chimpanzees that during primary HBV infection, liver damage occurs after the clearance of HBV and concomitantly with the massive infiltration of CD8 cells that is unlikely to be composed primarily of HBV-specific CD8 cells. In addition, using transgenic mice as recipients of HBV-specific cytotoxic T lymphocytes, liver damage was demonstrated to be due to the recruitment of lymphomononuclear cells into the liver, as a consequence of chemokines production by hepatocytes and other nonparenchymal cells.¹⁰ The finding that the neutralization of these chemokines is associated with maintenance of antiviral effects but diminished tissue damage suggests that an alternative therapy, aimed to block the effector arm of hepatocellular injury, could represent an effective approach to avoid the risk of progression, without hampering the chances of immune recovery from hepatitis B.

References

- 1 Chen PM, Chiou TJ, Fan FS *et al*. Fulminant hepatitis is significantly increased in hepatitis B carriers after allogeneic bone marrow transplantation. *Transplantation* 1999; **67**: 1425-1433.
- 2 Lau GKK, Liang R, Wu PC *et al*. Use of famciclovir to prevent HBV reactivation in HBsAg-positive recipients after allogeneic bone marrow transplantation. *J Hepatol* 1998; **28**: 359-368.
- 3 Perillo RP. Acute flares in chronic hepatitis B: the natural and unnatural history of an immunologically mediated liver disease. *Gastroenterology* 2001; **120**: 1009-1022.
- 4 Chiba T, Yokosuka O, Goto S *et al*. Successful clearance of hepatitis B virus after allogeneic stem cell transplantation: beneficial combination of adoptive immunity transfer and lamivudine. *Eur J Haematol* 2003; **71**: 220-223.
- 5 Lau GKK, Lok ASF, Liang RHS *et al*. Clearance of hepatitis B surface antigen after bone marrow transplantation: role of adoptive immunity transfer. *Hepatology* 1997; **25**: 1497-1501.
- 6 Colloredo Mels G, Bellati G, Leandro G *et al*. Quantitative analysis of IgM anti-HBc in chronic hepatitis B patients using a new 'gray-zone' for the evaluation of 'borderline' value. *J Hepatol* 1996; **25**: 644-648.
- 7 Strasser SI, McDonald SJ, Schoch G *et al*. Severe hepatocellular injury after hematopoietic cell transplant: incidence and etiology in 2136 consecutive patients. *Hepatology* 2000; **32**: 299A.
- 8 Guidotti LG, Rochford R, Chung J *et al*. Viral clearance without destruction of infected cell during acute HBV infection. *Science* 1999; **284**: 825-829.
- 9 Maini MK, Boni C, Lee CK *et al*. The role of virus specific CD8+ cells in liver damage and viral control during persistent hepatitis B virus infection. *J Exp Med* 2000; **191**: 1269-1280.
- 10 Kakimi K, Lane TE, Wieland S *et al*. Blocking chemokine responsive to gamma-2/interferon (IFN)-gamma inducible protein and monokine induced by IFN-gamma activity *in vivo* reduces the pathogenetic but not the antiviral potential of hepatitis B virus-specific cytotoxic T lymphocytes. *J Exp Med* 2001; **194**: 1755-1766.