Does OKT3 Increase the Risk of Recurrent Hepatitis B in Patients Transplanted for Hepatitis B?

Levels of HBV-DNA and HbsAg after acute liver allograft rejection treatment by corticoids and OKT3. *Gonzalez RA, de la Mata M, de la Torre J, Mino G, Pera C, Pena J, Munoz E.* Clin Transplant 2000:14:208-211. (Reprinted with permission.)

Abstract

The aim of this work was to analyze whether the treatment of acute rejection of orthotopic liver transplants (OLT), either with corticoids or OKT3, has any effect on levels of hepatitis B virus (HBV)-DNA and HbsAg in individuals which were originally affected by cirrhosis or fulminant hepatic failure as a result of B virus. We have found that HBV-DNA is present in macrophages, B cells and both CD4+ and CD8+ T cells after OLT in all cases studied. Interestingly, the levels of HBV-DNA and HbsAg in the serum analyzed were increased extremely rapidly in the patients treated with OKT3 in an acute rejection episode. However, the serum levels of HBV-DNA and HbsAg found were lower when the patients were treated with steroids, and were not found in non-treated patients. As the serum levels of HBV-DNA increase, the process of liver reinfection could be accelerated; therefore, these results may help to understand how OKT3 and corticoids immunosuppressive therapy may accelerate the reinfection of OLT by HBV. In conclusion, our results suggest that special care must be taken in the use of OKT3 in the treatment of acute liver rejection episodes in chronic or fulminant HBV transplanted patients.

Comments

Reactivation of hepatitis B virus (HBV) replication and exacerbation of liver disease have been reported in patients with chronic hepatitis B administered immunosuppressive or cytotoxic therapy.[1-3] Reactivation of HBV replication may occur not only in patients with replicative HBV infection (hepatitis B e antigen positive and detectable serum HBV DNA by non–polymerase chain reaction [PCR] assay), but also in patients with low or nonreplicative infection (hepatitis B e antigen negative and undetectable serum HBV DNA by non-PCR assay) and those with resolved infection (hepatitis B surface antigen [HBsAg] negative, antibody to HBsAg positive, and antibody to hepatitis B core antigen positive). This is related to the persistence of HBV, albeit at low levels, in the liver and circulating blood and the presence of HBV DNA in extrahepatic reservoirs, especially peripheral-blood mononuclear cells (PBMCs).[4,5]

Among the immunosuppressive agents used after orthotopic liver transplantation (OLT), corticosteroids may have the most potent effect on HBV replication. In addition to indirect effects through immunosuppression, corticosteroids may directly augment HBV replication through a glucocorticoid-responsive element in the HBV genome.[6] Other antirejection drugs, such as cyclosporine and tacrolimus, were reported to have no direct stimulatory effect on HBV replication.[7,8]

The effects of other antirejection therapies, such as OKT3 (Orthoclone OKT3; Ortho Biotech Inc, Raritan, NJ, and muromonab CD3), on HBV replication have not been studied. OKT3, a monoclonal antibody against T cells, induces a rapid lymphocytopenia generally attributed to lymphocyte opsonization and phagocytosis.[9,10] It also modulates the expression of the T-cell receptor complex so that T cells become blinded to the antigens presented by the allograft.[9,10] Furthermore, T-cell homocytolysis,[11] as well as apoptosis,[12] have been proposed as possible mechanisms of action of OKT3. The use of OKT3 in patients who underwent OLT for hepatitis C has been associated with early and severe recurrence of hepatitis C.[13,14]

In the study by Gonzalez et al,[15] 11 patients who underwent OLT for hepatitis B and developed acute rejection were studied. All patients were administered low-dose hepatitis B immune globulin (HBIG) intramuscularly (IM) as prophylaxis against HBV reinfection. No patient was administered antiviral therapy. Rejection episodes were treated with 3 doses of methylprednisolone and/or an increased dosage of oral prednisone. Steroid-resistant rejection episodes were treated with OKT3 for 10 to 14 days. Three patients were administered corticosteroids and OKT3, 6 patients were administered corticosteroids only, and 2 patients were not treated. All 3 patients treated with OKT3 developed high serum HBV DNA levels, and 2 of these patients died of recurrent hepatitis B during the second and third years post-OLT. Serum HBV DNA was present at low levels in 3 of the 6 patients treated with corticosteroids alone, but not in the 2 patients who were not treated. The investigators suggested that OKT3 may lead to a rapid increase in serum HBV DNA levels in patients who undergo OLT for hepatitis B and cautioned that special care be exercised when OKT3 is administered to these patients. They speculated that the devastating effects of OKT3 may be related to the release of viral particles secondary to lysis of T cells, release of cytokines that may facilitate entry of HBV into

hepatocytes and other cells, or activation of HBV replication within PBMCs by mitogens. These hypotheses are interesting and need to be tested. Although the investigators showed increasing serum HBV DNA levels in the 3 patients administered OKT3, the findings were based on a small number of patients tested at very few time points, and details about these 3 patients in relation to the other patients, such as total dose and duration of corticosteroid therapy and viral replication status before OLT and just before the rejection episode, were not provided. Thus, more data are needed to determine whether the use of OKT3 is associated with a more rapid increase in serum HBV DNA levels in patients who undergo OLT for hepatitis B.

Deciphering the mechanisms by which OKT3 increases serum HBV DNA levels is more difficult. Using PCR assay, the investigators found HBV DNA present in $CD4^+$ and $CD8^+$ T cells, B cells, and macrophages even before the rejection episode. It is possible that OKT3-mediated lysis of T cells results in the release of HBV DNA into the circulation. Whether lymphokines induced by OKT3 facilitated the entry of HBV into hepatocytes or promoted HBV replication is less certain. Currently, very few data exist on the mechanisms of entry of HBV into hepatocytes and other cells. Some of the lymphokines induced by OKT3, such as interferon-γ and tumor necrosis factor, have been shown to downregulate HBV expression.[16,17] Some studies suggested that HBV can replicate in PBMCs, but these findings are controversial.[18,19] It is more likely that the effects of OKT3 on HBV replication are mediated through reduced immune-mediated virus clearance through lymphocyte depletion and antigenic modulation of the T-cell receptor complex.

The important clinical question is what to do when patients who undergo OLT for hepatitis B develop an episode of rejection. It is obvious that these patients should continue to be administered prophylaxis for HBV reinfection. Currently, the most effective therapies include long-term, high-dose, intravenous HBIG or combination therapy with HBIG and lamivudine.[20,21] Because of the expense associated with high-dose intravenous HBIG, many centers are evaluating the efficacy of lower doses, shorter duration, or IM administration of HBIG in combination with lamivudine. The short-term efficacies of these regimens are impressive, but longer follow-up of a larger number of patients is needed to determine the most cost-effective prophylactic regimen for patients who undergo OLT for hepatitis B. The efficacy of IM HBIG alone has not been well documented and may account for the high reinfection rate reported by Gonzalez et al.[15] Even in patients administered adequate prophylaxis, the occurrence of rejection episodes necessitating more aggressive immunosuppressive therapy may increase the risks for HBV reinfection. In vitro studies using the human hepatoblastoma cell line showed that the addition of antiviral therapy can inhibit the increase in HBV replication induced by prednisolone and azathioprine.[7] It seems reasonable to consider the addition of lamivudine in patients administered HBIG monotherapy and closely monitor the antibody to HBsAg titer to determine whether greater or additional doses of HBIG should be administered to patients administered IM HBIG with or without lamivudine when patients who underwent transplantation for hepatitis B develop steroid-resistant rejection episodes necessitating OKT3 therapy.

Although significant progress has been made in the prevention of recurrent hepatitis B after OLT, much remains to be learned. Adequate prophylaxis should be administered to all patients, and close monitoring is required, especially in patients with replicative infection pre-OLT or who require more intense immunosuppression post-OLT. The effects of more selective antirejection drugs, such as anti–interleukin-2 receptor antibody, on HBV replication should be evaluated.

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Detecting Alcoholic Relapse Posttransplant

Carbohydrate-deficient transferrin is not a useful marker for the detection of chronic alcohol abuse. *Schmitt VM, Stieber P, Jungst D, Blizer M, Wachtler M, Heberger S.* Eur J Clin Invest 1998; 28:615-621. (Reprinted with permission.)

Abstract

Background: **The role of carbohydrate-deficient transferrin (CDT) as a reliable marker for the detection of chronic alcohol abuse has been discussed controversially.**
Methods: **Therefore, we investigated CDT in the sera from 405 subjects with different alcohol intake. Besides healthy control subjects (n = 42), inpatients and outpatients in a department of gastroenterology (n = 325) and patients admitted to a department of otorhinolarynology (n = 38) were studied. A total of 213 patients suffered from various forms of liver diseases, and 89 patients had liver transplantation. CDT values were determined by a double-antibody radioimmunoassay.**
Results: **In the 241 alcohol-abstinent subjects, CDT levels ranged from 3 to 90 units L^{-1} (median = 12); the 92 moderate drinkers (20-60 g of alcohol per day) showed values from 3 to 40 units L^{-1} (median = 12), and the 72 subjects with chronic alcohol abuse (> 60 g per day) revealed CDT levels from 3 to 100 units L^{-1} (median = 16). The diagnostic specificity for alcohol abuse was 86.8% for men (sensitivity 36.9%) and 95% for women (sensitivity 0%).**
Conclusion: **Our data indicate that measurement of CDT does not reach clinical use in the detection of chronic alcohol abuse in an unselected population because of its insufficient specificity and sensitivity.**

Comments

Alcohol-related liver disease accounts for up to 50% of the patients who die of end-stage liver disease.[1] Patients with alcoholic cirrhosis have posttransplantation survival rates similar to those for patients who undergo transplantation for non–alcohol-related liver disease.[2-4] However, relapse has been a significant concern in this population. Most studies report relapse rates after transplantation of 0% to 30%.[5] These studies used various definitions of relapse. Campbell et al[6] reported a small minority of patients who returned to problematic drinking, leading to rehospitalization and, in some cases, death.

The search for a way to detect alcohol use after transplantation has included developing biochemical markers that reliably detect relapse. Abnormalities in transferrin levels, later named carbohydrate-deficient transferrin (CDT), were found in the cerebrospinal fluid of patients with alcohol cerebellar degeneration in 1976,[7] and later, in the serum of alcohol abusers.[8] Since then, CDT has been studied as a marker of excessive