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HUMAN POLYCLONAL ANTI-HEPATITIS B SURFACE ANTIGEN IMMUNOGLOBULIN REDUCES THE FREQUENCY OF ACUTE REJECTION AFTER LIVER TRANSPLANTATION FOR CHRONIC HEPATITIS B

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SUMMARY

Background: Use of polyclonal anti-hepatitis B surface antigen immunoglobulin (HBIg) has been shown to reduce hepatitis B virus (HBV) recurrence after liver transplantation (LT) and to decrease the frequency of acute cellular rejection (ACR). However, the protective role of HBIg against ACR remains controversial, since HBV infection has been also associated with a lower incidence of ACR. **Aim**: To assess the relationship between HBIg immunoprophylaxis and the incidence of rejection after LT. **Methods**: 260 patients (158 males, 43 ± 14 years old) submitted to LT were retrospectively evaluated and divided into three groups, according to the presence of HBsAg and the use of HBIg. Group I was comprised of HBsAg-positive patients (n = 12) that received HBIg for more than 6 months. Group II was comprised of HBsAg-positive patients that historically have not received HBIg or have been treated irregularly for less than 3 months (n = 10). Group III was composed of 238 HBsAg-negative subjects that have not received HBIg. **Results**: HBIg-treated patients (group I) had significantly less ACR episodes, when compared to group II and III. No differences between groups II and III were observed. **Conclusions**: Long-term HBIg administration contributes independently to reduce the number of ACR episodes after LT.

KEYWORDS: HBIg; Acute hepatic rejection; Liver transplantation; Chronic hepatitis B.

INTRODUCTION

Long-term prophylactic administration of polyclonal anti-hepatitis B surface antigen immunoglobulin (HBIg) has been shown to reduce hepatitis B virus (HBV) recurrence and to improve survival after liver transplantation (LT) for chronic hepatitis B (CHB)[7,8,13], as well as to decrease the frequency of HCV viremia after LT in patients with hepatitis B and C coinfection[4]. Apart from its effect on recurrent viral diseases, HBIg administration was also associated with lower incidence of acute hepatic rejection (ACR) and chronic ductopenic rejection (CDR) after LT[3]. In this respect, patients submitted to liver transplantation for CHB were shown to be less susceptible to both ACR and CDR than non-HBV transplanted subjects[1,3]. However, it is not yet clear whether this reduced rate of rejection observed in those patients is related, in fact, to HBV infection or to the long-term administration of HBIg.

The purpose of the present study was to investigate the relationship between HBIg immunoprophylaxis and the incidence of ACR and CDR in patients with CHB submitted to LT with and without HBIg immunoprophylaxis.

PATIENTS AND METHODS

Subjects: Two-hundred and sixty patients (158 males, 43 ± 14 years old) that underwent liver transplantation between September 1985 and June 1999 were retrospectively evaluated and divided into three groups according to the presence of HBsAg and the use of HBIg. Twenty-two patients had CHB of whom all were HBsAg positive, and nine had HBeAg. Group I was comprised of HBsAg-positive patients who received HBIg for more than 6 months to achieve HbsAb levels ≥ 100 IU/L (n = 12). Group II was composed of HBsAg-positive patients who historically have not received HBIg immunoprophylaxis (n = 7) or had been treated irregularly with HBIg for less than 3 months (n = 3). Group III included 238 HBsAg-negative subjects who underwent LT due to other chronic liver diseases.

The frequencies of ACR and CDR and the number of ACR episodes during the first six months after liver transplantation were recorded in all patients.

Immunosuppressive regimen: All patients used triple-drug immunosuppression that consisted of cyclosporin, prednisone and

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azathioprine. All acute allograft rejection episodes were treated with intravenous bolus of 1-3 g of methylprednisolone with or without an oral recycle of prednisone. All acute allograft rejection episodes that were resistant to corticosteroid therapy were subsequently treated with OKT3.

HBIg regimen: Immunoprophylaxis with HBIg was begun during the anhepatic phase with 10,000 IU of HBIg intravenously. The frequency of HBIg administration was based on the HBsAb titers for maintaining levels above 100 IU/L in the long-term follow-up. As previously stated, all patients in group I received HBIg therapy for more than six months, while three patients in group II received immunoprophylaxis for no longer than three months.

Diagnosis of rejection: The diagnosis of ACR was based on the presence of abnormal liver enzymes and pathological evidence of rejection that included the presence of mixed portal infiltrate associated with bile duct and/or endothelial cell injuries. CDR was defined by the histological findings of vanishing interlobular bile ducts in greater than 50% of the portal tracts and/or histological findings of foam cell arteriopathy[2].

Statistical analysis: The cumulative rate of ACR and CDR and the frequency of ACR episodes in the first six months after LT were determined in patients from groups I, II and III, and were compared using either the Kruskal-Wallis test or the Fisher exact probability test, when appropriate. A p value < 0.05 was considered significant. Clinical and laboratory data are expressed in text and tables as percentages or median and range.

RESULTS

The frequency of ACR in groups I, II and III at six months was 25%, 70% and 56%, respectively (p = NS) (Table 1).

Table 1
Frequency of acute cellular rejection in groups I, II and III

	N	Frequency of acute cellular rejection
Group I	3	25%
Group II	7	70%
Group III	133	56%

p = NS

Patients treated with HBIg (group I) had significantly less ACR episodes when compared to group II (0.3 ± 0.5 vs. 0.9 ± 0.7, p = 0.02) and group III (0.3 ± 0.5 vs. 0.7 ± 0.7, p = 0.03). No differences between groups II and III were observed (Table 2).

Table 2
Number of acute cellular rejection episodes in groups I, II and III

	Number of AHR episodes
Group I	0.3 ± 0.5^{a}
Group II	0.9 ± 0.7^{b}
Group III	0.7 ± 0.7^{c}

^{a,b} p = 0.02, ^{a,c} p = 0.03

Time interval until the first episode of rejection, rates of steroid-resistant rejection and CDR were not statistically different between those groups (Table 3).

Table 3
Timing of the first acute allograft rejection episode and frequencies of steroid-resistant acute rejection and chronic rejection in groups I, II and III

	Timing of the first episode of acute allograft rejection (days)	Steroid-resistant Acute rejection (%)	Chronic ductopenic rejection (%)
Group I	6.9 [6.9-6.9]	0	0
Group II	8.1 [6.0-12.9]	0	0
Group III	6.9 [3.0-99]	12%	4%

p = NS

DISCUSSION

The findings of the present study indicate that the use of HBIg, for the purpose of preventing recurrence of hepatitis B after LT, is also associated with fewer episodes of ACR in the first six months after surgery. The cumulative incidence of ACR was also shown to be reduced in HBIg-treated subjects, when compared to other patients submitted to LT, but the difference was not significant. The decrease in the number of ACR was related to HBIg administration and not to previous CHB and/or HBV recurrence following LT, because no differences in the frequency of ACR episodes were noted between patients submitted to LT for hepatitis B, who had not been treated with HBIg, and patients transplanted with other chronic liver disorders.

Two previous studies have reported reduced frequencies of rejection in patients submitted to LT for hepatitis B, but were unable to distinguish whether these findings were secondary to HBIg administration or to previous hepatitis B infection, and/or recurrence after LT[1,3].

ADAMS *et al.*[1] have reported lower rates of ACR in patients submitted to LT due to chronic hepatitis B but the authors have not examined the possible role of HBIg in this setting. Additionally, FARGES *et al.*[3] have investigated the frequency of hepatic allograft rejection in patients submitted to LT due to CHB and other chronic liver diseases, including alcoholic liver disease (ALD), primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, and chronic hepatitis C. Most of the patients with CHB were HBV DNA negative and have received long-term HBIg immunoprophylaxis with no signs of HBV recurrence on the graft. The actuarial incidence of ACR and CDR was significantly decreased in the patients transplanted for CHB, when compared to subjects with other chronic liver diseases. The frequency of ACR, but not CDR, was also reduced in patients with ALD prior to LT. As this decrease was associated with an increase in septic complications, it was hypothesized that the decreased rate of ACR observed in this group of patients could be due to diminished immune responsiveness, possibly related to previous alcohol consumption. In respect to patients transplanted for CHB, the only possibility raised by the authors to explain the observed lower frequency of ACR was the use of polyclonal immunoglobulins. In this regard, a reduced incidence of

ACR, but not of CDR, was also associated, in the same study, with the prophylactic use of polyclonal anti-cytomegalovirus immunoglobulin[3].

The reasons for the reduced rates of ACR observed in HBIg-treated patients remain largely unknown. The use of human polyclonal immunoglobulins has been previously shown to influence the timing of experimental hyperacute xenograft rejection and to decrease *in vivo* and *in vitro* T cell responses in sensitized renal transplant candidates[5,9,10]. These effects are possibly due to the presence of anti-idiotypes in these preparations directed against preformed antidonor antibodies[9]. However, HBIg therapy has been associated with reduced rates of ACR, that is thought to be mediated by cytotoxic T cells against donor alloantigens and not by preexisting antidonor antibodies[14]. It is well known that polyclonal antilymphocyte immunoglobulins and monoclonal anti-CD3 antibodies are effective agents used in the prevention and the treatment of ACR, because of their marked effect on circulating cytotoxic T cells[11]. It is therefore possible to speculate that polyclonal immunoglobulin preparations could influence to a lesser extent cytotoxic T cell responses through similar immunoregulatory properties.

These findings all together, suggest that HBIg administration may contribute to reduce the number of ACR episodes after LT. This reduction seems to be related to HBIg prophylaxis since HBsAg-positive patients who did not receive HBIg in the present study had similar rates of rejection, when compared to their HBsAg-negative counterparts. However, it is important to emphasize that other studies evaluating the influence of etiology in the frequency of rejection have not shown reduced rates of rejection in patients transplanted for CHB[14,15]. As those reports have not addressed the influence of HBIg prophylaxis on the frequency of ACR, it would be therefore interesting to reassess the effect of HBIg therapy in this setting.

Several centers are now employing lamivudine alone or in association with HBIg prophylaxis for the prevention of HBV recurrence on the graft[6,12]. It would be very interesting to compare the incidence of rejection in those subjects receiving either lamivudine or HBIg prophylaxis after LT in order to settle this issue.

RESUMO

A imunoglobulina policlonal humana anti-antígeno de superfície da hepatite B reduz a freqüência da rejeição aguda após transplante de fígado

Introdução: O emprego da imunoglobulina policlonal anti-antígeno de superfície da hepatite B (HBIg) tem reduzido a recorrência da hepatite B após transplante hepático (TH), assim como também a freqüência de rejeição celular aguda (RCA). No entanto, o papel protetor da HBIg contra a RCA permanece controverso, pois a própria infecção por vírus B foi também associada a menor incidência de RCA. **Objetivos**: Verificar a relação entre HBIg e a freqüência de RCA após TH. **Métodos**: 260 pacientes (158 do sexo masculino, com 43 ± 14 anos) submetidos a TH foram avaliados, retrospectivamente, e divididos em três grupos de acordo com a presença de AgHBs e uso de HBIg. O grupo I foi constituído por 12 pacientes com AgHBs que receberam HBIg por mais de 6 meses; o grupo II foi formado por 10 pacientes com AgHBs que não receberam HBIg regularmente; o grupo III foi composto por 238 indivíduos sem AgHBs que não receberam HBIg. **Resultados**: Nos pacientes do grupo I houve freqüência significantemente menor de episódios de RCA, em comparação ao que se observou nos grupos II e III. Nenhuma diferença ocorreu entre os grupos II e III. **Conclusões**: A administração profilática de HBIg contribui independentemente para reduzir a freqüência dos episódios de RCA após a realização de TH.

REFERENCES

1. ADAMS, D.H.; HUBSCHER, S.G.; NEUBERGER, J.M. *et al.* - Reduced incidence of rejection in patients undergoing liver transplantation for chronic hepatitis B. **Transplant. Proc., 23:** 1436-1437, 1991.

2. DEMETRIS, A.J.; BATTS, K.P.; DHILLON, A.P. *et al.* - Banff schema for grading liver allograft rejection: an international consensus document. **Hepatology, 25:** 658-666, 1997.

3. FARGES, O.; SALIBA, F.; FARHAMANT, H. *et al.* - Incidence of rejection and infection after liver transplantation as a function of the primary disease: possible influence of alcohol and polyclonal immunoglobulins. **Hepatology, 23:** 240-248, 1996.

4. FERAY, C.; GIGOU, M.; SAMUEL, D. *et al.* - Incidence of hepatitis C in patients receiving different preparations of hepatitis B immunoglobulins after liver transplantation. **Ann. intern. Med., 128**: 810-816, 1998.

5. LATREMOUILLE, C.; GENEVAZ, D.; HU, M.C. *et al.* - Normal human immunoglobulins for intravenous use (IVIg) delay hyperacute xenograft rejection through F(ab')2-mediated anti-complement activity. **Clin. exp. Immunol., 110:** 122-126, 1997.

6. LOK, A.S.; HEATHCOTE, E.J. & HOOFNAGLE, J.H. - Management of hepatitis B: 2000. Summary of a workshop. **Gastroenterology, 120:** 1828-1853, 2001.

7. SAMUEL, D.; MULLER, R.; ALEXANDER, G. *et al.* - Liver transplantation in European patients with hepatitis B surface antigen. **New Engl. J. Med., 329:** 1842-1847, 1993.

8. SAWYER, R.G.; MCGORY, R.W.; GAFFEY, M.J. *et al.* - Improved clinical outcomes with liver transplantation for hepatitis B-induced chronic liver failure using passive immunization. **Ann. Surg., 227:** 841-850, 1998.

9. SCHUSSLER, O.; GENEVAZ, D.; LATREMOUILLE, C. *et al.* - Intravenous immunoglobulins for therapeutic use contain anti-idiotypes against xenophile antibodies and prolong discordant graft survival. **Clin. Immunol. Immunopath., 86:** 183-191, 1998.

10. SIVASAI, K.S.; MOHANAKUMAR, T.; PHELAN, D. *et al.* - Cytomegalovirus immune globulin intravenous (human) administration modulates immune response to alloantigens in sensitized renal transplant candidates. **Clin. exp. Immunol., 119:** 559-565, 2000.

11. TAYLOR, R.M. - Monoclonal and polyclonal antibodies: clinical aspects. **Immunol. Lett., 29:** 113-116, 1991.

12. TERRAULT, N. - Hepatitis B and liver transplantation. **Clin. Liver Dis., 3:** 389-415, 1999.

13. TERRAULT, N.A.; ZHOU, S.; COMBS, C. *et al.* - Prophylaxis in liver transplant recipients using a fixed dosing schedule of hepatitis B immunoglobulin. **Hepatology, 24:** 1327-1333, 1996.

14. VIERLING, J.M. - Immunology of acute and chronic hepatic allograft rejection. **Liver Transpl. Surg., 5**(suppl. 1): S1-S20, 1999.

15. WIESNER, R.H.; DEMETRIS, J.; BELLE, S.H. *et al.* - Acute hepatic allograft rejection: incidence, risk factors, and impact on outcome. **Hepatology, 28:** 638-645, 1998.

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