Evolution of patients undergoing liver transplantation due to viral hepatitis

ABSTRACT

Objectives: to describe the evolution of patients with a diagnosis of viral hepatitis B or C undergoing liver transplantation at a reference hospital. Methods: this was a cross-sectional study conducted in the Organ Transplantation Service of the Alfa Institute of Gastroenterology, General Hospital, Federal University of Minas Gerais, from 2005 to 2007. Data were collected from medical records and service databases. Results: out of 173 patients undergoing liver transplantation, 61 had hepatitis C, nine had hepatitis B, and one developed fulminant hepatitis A. Among patients with hepatitis C, 31 were treated before the transplantation (seven with sustained virological response). Only two patients with hepatitis B were pretreated. After liver transplantation, the recurrence of hepatitis occurred in 21 patients with hepatitis C, and in none with hepatitis B. The drug treatment after liver transplant was performed in 13 out of 21 patients with recurrent hepatitis C. Discussion: in cases of cirrhosis caused by the hepatitis C virus, recurrence of infection is common after liver transplantation and indicates the need for an effective treatment. Post-transplant survival in patients infected with hepatitis B virus depends on prevention using combined prophylaxis. Conclusion: viral hepatitis accounts for a significant proportion of indications for a liver transplant. Recurrence of hepatitis C persists as a major problem in transplanted patients due to viral hepatitis. Prophylaxis of hepatitis B post-transplant recurrence is mandatory with immunoglobulin and nucleoside analogs. Key words: Hepatitis, Viral, Human; Hepatitis B; Hepatitis C; Liver Transplantation.

RESUMO

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In Brazil, the number of patients eligible for a liver transplant in the waiting list was 5,847 in 2012; 1,595 liver transplants were performed in the country in 2012, with 1,478 using cadaveric donor grafts. The average time on the waiting list in Brazil in 2012 was 19 months; the mortality rate of patients on the waiting list was about 30%. From 2005 to 2008, the average number of patients on the waiting list for liver transplantation was 6,775 per year. However, the number of effective donors in 2007 was 1,150 despite the existence of 5,494 potential donors, totaling 1,025 transplants performed in the same year.

Due to the high number of patients with chronic liver disease progressing to organ failure and the consequent increase in the demand for liver donors, this article aims to describe the population undergoing liver transplantation diagnosed with viral hepatitis B or C in a reference center.

METHODS

This is a descriptive and cross-sectional study conducted in the Organ Transplantation Service of the Alfa Institute of Gastroenterology, in the General Hospital (HC) of the Federal University of Minas Gerais (UFMG) from January of 2005 to December of 2007. Information was collected from all patients who underwent liver transplantation during the study period, diagnosed with hepatitis B or C, and followed-up until 2009. The diagnosis of hepatitis A was defined by IgM anti-VHA serology; hepatitis B was defined by HBsAg positive serology or positive DNA PCR for B virus, and hepatitis C by AntiHCV positive serology confirmed by positive RNA PCR for the C virus.

The drugs used and the evolution of viral load were assessed after treatment; a sustained virological response was considered a good therapeutic response. Data were collected retrospectively from medical records, the Transplant Group databases, and Hospital Infection Control Commission (CCIH) of HC/UFMG.

The analyzed variables were: gender, age, bilirubins (total and direct), albumin, prothrombin activity, RNI, creatinine, ascites, encephalopathy, ratings on Child-Turcotte-Pugh (CTP), the pre-transplant Model for End-Stage Liver Disease (MELD), and infectious complications in the post-transplant.

Data were stored and analyzed in the statistical programs Excel 2003 and SPSS version 13.0. The descriptive analysis included frequency and per-
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Out of the 31 patients with hepatitis C, who received treatment, seven (23%) showed a sustained virological response and 24 (77.4%) showed no response. Compared to patients with hepatitis B, the two who were treated, one showed a good therapeutic response (Figure 1). The mean duration of treatment was 7.2 (± 6.3) months.

Recurrence after treatment was noted in four patients, three of whom had hepatitis C and one hepatitis B (Figure 2).

Among the 18 who did not respond to the initial treatment and those who relapsed, a new drug treatment was performed. In 10 patients with hepatitis C, the main association was pegylated interferon and ribavirin (Table 3); among those patients with HBV hepatitis, two received the new treatment: adefovir in one patient, and adefovir-associated with lamivudine in another.

After liver transplantation, viral relapse was again evaluated in 33 previously treated patients and observed in 21 patients with hepatitis C, and in none with hepatitis B (Figure 3). Prophylaxis with immuno-
DISCUSSION

According to the ABTO, the most frequent indication for liver transplantation is cirrhosis, which has the chronic use of alcohol and hepatitis viruses as the main causes. These data were also similar to those of European liver transplant records, which showed 50% indications for transplant due to cirrhosis. Out of these, 16% were related to HCV infection and 18% to alcohol abuse. Spite of hepatitis viruses being related to the main indications for transplant, there is a high degree of geographic variation in their distribution. HCV is the most important etiological agent in Western Europe, North America, and Egypt, and HBV is the most important in South Africa, Latin America, Central Asia, and Taiwan. These data corroborate the importance of better understanding the population undergoing liver transplantation due to hepatitis B and C.

In this study, the main indication for liver transplantation were viral hepatitis (41%), and 85.9% were due to HCV.

Treatment with pegylated interferon and ribavirin, more recently associated with protease inhibitors, is the treatment of choice for patients with hepatitis C, although the response is lower in patients with cirrhosis and the treatment is contraindicated before the evidence of decompensated cirrhosis due to its high risk. In this study, the major therapeutic regimens for the treatment of hepatitis C were interferon in combination with ribavirin (39%), pegylated interferon combined with ribavirin (23%), and interferon monotherapy (23%). The therapy was based on the viral hepatitis treatment protocol of the Brazilian Ministry of Health.

After liver transplantation for HCV-related cirrhosis, the recurrence of HCV infection occurs in virtually all patients with an increase of 10 to 20 times in the levels of viremia. Graft hepatitis occurs in most patients with viremia.
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cases accompanied by at least five years.\textsuperscript{14-18} The progression of this hepatitis is accelerated in those transplanted towards immunocompetent patients, i.e., it was observed that 6 to 23% of these develop cirrhosis within three to four years after the transplant,\textsuperscript{14-21} with a cumulative probability of progression to cirrhosis in up to 30% in five years post-transplant.\textsuperscript{22} The progression of fibrosis and liver disease related to hepatitis C after liver transplantation is significantly faster than that observed in immunocompetent patients.\textsuperscript{30} The development of cirrhosis is associated with reduced survival of graft and patient. These differences in the progression of hepatitis C in liver transplantation receptors which are immunocompromised and immunocompetent are present not only before the development of cirrhosis but also after the established cirrhosis with a high risk of clinical decompensation. Currently, in most liver transplantation centers in the world, protocol liver biopsies are held at regular intervals after liver transplantation, and once detected alterations of chronic hepatitis B after fibrosis, the treatment is carried out with antivirals. Treatment is conducted with pegylated interferon and ribavirin and, more recently, the association of these drugs with protease inhibitors (boceprevir, telaprevir) has enabled better results on the sustained virological response.\textsuperscript{21-23}

HBV infection is an important cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma worldwide. The long-term survival after a liver transplantation period in patients infected with HBV depends on preventing graft re-infection by the virus. In the absence of preventive measures, the risk of graft re-infection can reach 80%, and infection can lead to graft dysfunction, the need for re-transplantation, and death.\textsuperscript{24,25} Over the recent years, much progress has been made in the treatment of hepatitis B and prevention of its recurrence after liver transplantation. Initially, the prolonged use of hyperimmune anti-HBs globulin (HBIG) after transplantation has enabled the reduction of overall recurrence rates of B viral infection in 20% -36%.\textsuperscript{26-28} However, re-infection rates remained high in high-risk patients or those with viral B cirrhosis with the high pre-transplant viral load.\textsuperscript{26,29,30} The availability of effective antiviral agents, such as lamivudine, adefovir, dipivoxil, entecavir, and tenofovir and the use of prophylaxis of these agents combined with HBIG provided significant improvements in results, even in high-risk groups, with a reduction of re-infection rates to approximately 10%.\textsuperscript{29,31-35}

CONCLUSION

Viral hepatitis accounts for a significant proportion of indications for liver transplant in Brazil (41%) and, among these, most are diagnosed with viral C liver cirrhosis. The recurrence of hepatitis C persists as the major problem in transplanted patients due to viral hepatitis. Treatment with pegylated interferon combined with ribavirin and, more recently, with protease inhibitors, represents a therapeutic option that is currently available. The prophylaxis of post-transplant recurrent hepatitis B is mandatory and highly effective when the combination of HBIG and nucleotides analogues is used providing great results.

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