

# Evolution of patients undergoing liver transplantation due to viral hepatitis

## *Evolução de pacientes submetidos a transplante hepático por hepatites virais*

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### 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

**Objetivos:** descrever a evolução dos pacientes com diagnóstico de hepatite viral B ou C submetidos a transplante de fígado em serviço de referência. **Métodos:** trata-se de estudo transversal realizado no Serviço de Transplante de Órgãos do Instituto Alfa de Gastroenterologia do Hospital das Clínicas da Universidade Federal de Minas Gerais, de 2005 a 2007. Os dados foram coletados em prontuários médicos e bancos de dados do serviço. **Resultados:** de 173 pacientes submetidos a transplante de fígado, 61 apresentavam hepatite C, nove tinham hepatite B e um evoluiu com hepatite A fulminante. Entre os pacientes com hepatite C, 31 receberam tratamento antes do transplante (sete com resposta virológica sustentada). Apenas dois pacientes com hepatite B foram tratados previamente. Após transplante hepático, a recidiva da hepatite ocorreu em 21 pacientes com hepatite C e nenhum com hepatite B. O tratamento medicamentoso após transplante hepático foi realizado em 13 de 21 dos pacientes com recidiva de hepatite C. **Discussão:** após transplante hepático em casos de cirrose pelo vírus da hepatite C, a recorrência da infecção é comum e indica necessidade de tratamento efetivo. A sobrevida pós-transplante em pacientes infectados pelo vírus da hepatite B depende da prevenção com uso da profilaxia combinada. **Conclusão:** as hepatites virais respondem por importante proporção

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*das indicações de transplante de fígado. A recidiva da hepatite C persiste como o principal problema nos pacientes transplantados por hepatites virais. A profilaxia da recidiva da hepatite B pós-transplante é mandatória com imunoglobulina e análogos de nucleosídeos.*

*Palavras-chave: Hepatite Viral Humana; Hepatite B; Hepatite C; Transplante de Fígado.*

## INTRODUCTION

Chronic liver diseases are responsible for 1.4 million deaths annually worldwide, including 796,000 due to cirrhosis and 616,000 to primary liver cancer.<sup>1</sup>

Viral hepatitis represents a serious public health problem in Brazil and worldwide. The World Health Organization estimates that there are over 240 million hepatitis B and 150 million hepatitis C chronic carriers, with approximately two and three million in Brazil, respectively.<sup>1,3</sup>

Infection with hepatitis B virus (HBV) affects about 2 billion people who have had contact with the virus worldwide, which is estimated to be associated with 600,000 deaths per year.<sup>4,1</sup> Its chronic evolution occurs in approximately 5-10% of infected adults and 90% of infections in children under five years old. The special feature of the chronic HBV infection is the possibility of developing into liver cancer regardless of the occurrence of cirrhosis, which is considered a prerequisite for the emergence of hepatocellular carcinoma in other chronic viral infections such as hepatitis C.<sup>2</sup>

Infection with hepatitis C virus (HCV), in turn, affects about 2% of the world population. It is considered the leading cause of liver disease and morbidity and mortality from chronic liver diseases. Progression of chronic infection occurs in 70-85% of cases, with one-quarter to one-third of these cases potentially progressing to severe histological forms or cirrhosis after 20 years if no therapeutic intervention occurs. At least 20% of deaths from chronic liver diseases are attributed to HCV infection, reaching more than 280,000 deaths per year.<sup>5-7</sup>

Thus, HCV or HBV infections result in the need for greater number of liver transplants because the chronic forms have a high risk of progression to cirrhosis, hepatic decompensation, and hepatocellular carcinoma.<sup>3</sup>

Currently, liver transplantation is the most effective therapy for patients in the terminal stage of chronic liver diseases. However, the number of patients on the waiting list for liver transplantation has increased considerably in the last decade.<sup>8</sup>

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%.<sup>9</sup> 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.<sup>9</sup>

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-

centage distribution for categorical variables and average calculation and standard deviation for quantitative variables.

The study was approved by the Research Ethics Committee (COEP) of UFMG.

## RESULTS

From January of 2005 to December of 2007, 173 patients underwent liver transplantation at the HC-UFMG. A total of 61 were diagnosed with hepatitis C (35.3%), nine with hepatitis B (5.2%), and one with hepatitis A (0.6%); 102 (58.9%) patients had no viral hepatitis. The transplantation diagnoses are indicated in Table 1.

**Table 1** - Liver transplant indication according to the diagnosis in the HC/UFMG from 2005-2007

Diagnoses	Number of patients	%
Viral hepatitis	71	41
Cryptogenic cirrhosis	30	17.3
Ethanol cirrhosis	18	10.4
Autoimmune cirrhosis	13	7.5
Cirrhosis due to biliary atresia	6	3.5
Fulminant hepatitis	5	2.9
Primary biliary cirrhosis	4	2.3
Primary sclerosing cholangitis	4	2.3
Others	22	12.7
<b>Total</b>	<b>173</b>	<b>100</b>

Among the 71 patients with viral hepatitis, the average age was 54.7 ( $\pm$  10.2) years, with a median of 56 (10-74) years. Regarding the CTP score, 13 (18.3%) ranked A, 17 (24%) ranked B, and 36 (50.7%) ranked C while the MELD showed an average of 14.8 ( $\pm$  6.6) with a median of 15 (2-36).

The indication for transplant occurred in 61 (85.9%), nine (12.7%), and one (1.4%) patients due to hepatitis C, hepatitis B, and fulminant hepatitis A, respectively. Among the 61 patients with hepatitis C, 27 (51%) received medical treatment before transplantation; in four patients it was not possible to obtain information about which drug was prescribed, and 30 received no treatment. Data on therapeutic regimens are shown in Table 2.

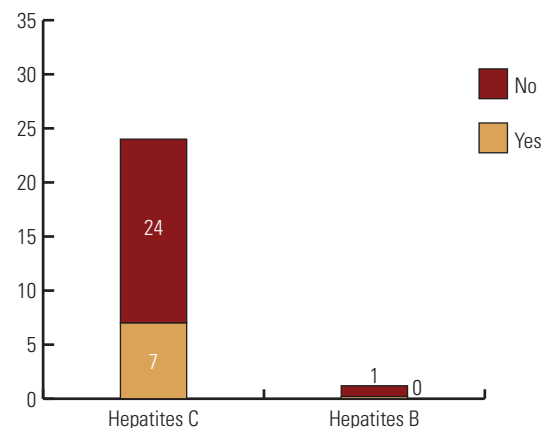
Among patients diagnosed with hepatitis B, two received treatment with lamivudine before transplantation, and seven received no treatment.

**Table 2** - Medication used in the treatment of hepatitis C prior to liver transplantation at the HC/UFMG 2005-2007

Medication	Number of patients	%
Interferon associated with ribavirin	12	44
Pegylated interferon associated with ribavirin	7	26
Interferon	7	26
Pegylated interferon	1	4
<b>Total</b>	<b>27</b>	<b>100</b>

It was not possible to inform the medication used in four patients.

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 ( $\pm$  6.3) months.



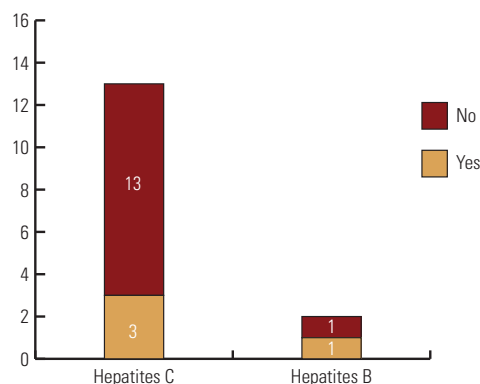
**Figure 1** - Number of cases of hepatitis B and C distributed according to response to treatment, HC/UFMG from 2005 to 2007.

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-

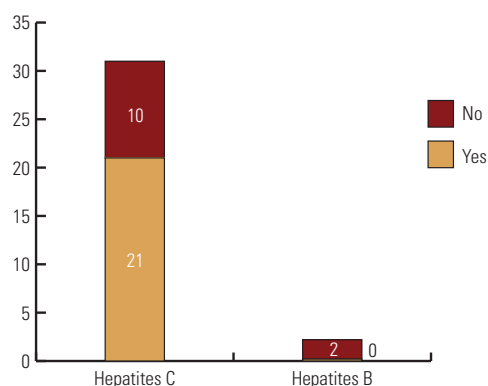
globulin was performed in all patients with hepatitis B after transplantation.



**Figure 2** - Number of cases of hepatitis B and C distributed according to recurrence after treatment, HC/UFMG from 2005 to 2007.

**Table 3** - Medication used in the re-treatment of hepatitis C prior to liver transplantation at the HC/UFMG 2005-2007

Medication	Number of patients	%
Pegylated interferon associated with ribavirin	5	50
Interferon associated with ribavirin	2	20
Pegylated interferon associated with ribavirin and amantadine	1	10
Pegylated interferon	1	10
Interferon	1	10
<b>Total</b>	<b>10</b>	<b>100</b>



**Figure 3** - Number of cases of hepatitis B and C distributed according to recurrence after liver transplantation, HC / UFMG from 2005 to 2007.

Drug treatment of viral recurrence after liver transplantation was carried in 13 (61.9%) out of 21 patients who showed relapsed hepatitis C by using pegylated interferon combined with ribavirin in the majority (54%). Table 4 presents all used regimens.

**Table 4** - Medication used in the treatment of re-current hepatitis C prior to liver transplantation at the HC/UFMG 2005-2007

Medication	Number of patients	%
Pegylated interferon associated with ribavirin	7	64
Interferon associated with ribavirin	2	18
Pegylated interferon associated with ribavirin and amantadine	1	9
Interferon	1	9
<b>Total</b>	<b>11</b>	<b>100</b>

It was not possible to inform the medication used in two patients.

## 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.<sup>10</sup> 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.<sup>11</sup> 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.<sup>12</sup> 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.<sup>2,13</sup>

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

cases accompanied by at least five years.<sup>14-18</sup> 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,<sup>14-21</sup> with a cumulative probability of progression to cirrhosis in up to 30% in five years post-transplant.<sup>22</sup> The progression of fibrosis and liver disease related to hepatitis C after liver transplantation is significantly faster than that observed in immunocompetent patients.<sup>16</sup> The development of cirrhosis is associated with reduced survival of graft and patient. These differences in the progression of hepatitis C in liver transplantation recipients 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 before 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.<sup>21-23</sup>

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.<sup>24,25</sup> 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%.<sup>26-28</sup> However, reinfection rates remained high in high-risk patients or those with viral B cirrhosis with the high pre-transplant viral load.<sup>26,29,30</sup> 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 reinfection rates to approximately 10%.<sup>29,31-35</sup>

## 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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