ARTIGO ORIGINAL

Recurrent hepatitis C virus following liver transplantation

Recidiva da hepatite C após transplante de fígado

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Resumo

Introdução: A recidiva da infecção pelo vírus da hepatite C após transplante de fígado é universal. **Objetivo:** Descrever a recidiva da hepatite C após transplante de fígado e a resposta virológica sustentada à terapia antiviral. **Casuística e Métodos:** Coorte retrospectiva de pacientes transplantados de fígado entre 1998 e 2010, por cirrose por vírus C. Excluídos aqueles sem biópsia pós-transplante e dados insuficientes no prontuário. Recidiva da hepatite C foi definida como positividade sérica de HCV RNA e evidência histológica de hepatite na biópsia hepática; a primeira biópsia hepáticapós-transplante com evidências histológicas de dano viral foi usada para determinar o tempo de recidiva. Estatística: Teste *t-Student*, teste qui-quadrado, teste exato de Fisher e Kaplan-Meier. **Resultados:** De 147 pacientes transplantados com vírus C, foram incluídos 80 pacientes no estudo. Etiologia da cirrose: vírus hepatite C + álcool 40,5%; vírus hepatite C isolado 32,4%; vírus hepatite C + álcool + vírus hepatite B 20,3%; vírus hepatite C + vírus hepatite B 6,8%. Genótipos 1,2 e 3 foram 67%, 10% e 23%, respectivamente. Imunossupressão: prednisona 97%, azatioprina 79%, ciclosporina 71%. Evidência histológica de recidiva da hepatite C em 40 de 56 pacientes (71%) submetidos à biópsia hepática nos primeiros 6 meses após o transplante. Sobrevida mediana livre de recidiva foi 11,6 meses. Terapia antiviral: 35 pacientes (Interferon+ribavirina 35% ou Peginterferon+ribavirina 65%). Resposta virológica sustentada: 44% (32% para genótipo 1 e 70% para genótipo não-1, p=0,04). Efeitos colaterais principais: anemia 79%, leucopenia 68%, trombocitopenia 64%; transfusão sanguínea necessária em 30%.**Conclusão:** Recidiva da hepatite C em transplantados de fígado ocorreu rapidamente. Terapia antiviral foi pouco tolerada e obteve baixa taxa de resposta virológica sustentada. Esses dados enfatizam a necessidade de novas drogas, mais efetivas e seguras, na busca pela erradicação do vírus C tanto antes, quanto após o transplante de fígado.

Descritores: Hepatite C; Fígado; Transplante.

Abstract

Introduction: Recurrence of hepatitis C virus is universal after liver transplantation. **Objective:** Describe the recurrence of hepa-titis C after liver transplantation and sustained virological response to antiviral therapy. **Patients and Methods:** We carried out a retrospective cohort of liver transplant recipients from 1998 to 2010 due to cirrhosis caused by hepatitis C virus. Patients without post-transplant liver biopsy or whose medical records lacked data were excluded. Hepatitis C recurrence was defined by the posi-tivity of serum hepatitis C virus RNA and histological evidence of hepatitis at liver biopsy. The first liver biopsy with histological parameters of viral damage was considered for diagnosis of time of hepatitis recurrence. To analyze data we used Student t-test, qui-square test, Fisher exact test, and Kaplan-Meier method. **Results**: From 147 liver transplant recipients, 80 patients were included in the study. Cirrhosis etiology: hepatitis C virus +alcohol 40.5%; hepatitis C virus 32.4%; hepatitis C virus +alcohol+ hepatitis B virus20.3%; hepatitis C virus + hepatitis B virus 6.8%. Hepatitis C virus genotypes 1, 2, and 3 were 67%, 10% and 23%, respec-tively. Immunosuppression: prednisone 97%; azathioprine 79%; cyclosporine 71%. There was histological evidence of hepatitis C recurrence in 40 of 56 patients (71%) subjected to liver biopsy within the first 6 months following liver transplantation. Median disease-free survival was 11.6 months. Antiviral therapy: 35 patients (Interferon+ribavirin 35% or Pegylated interferon+ribavirin 65%). Sustained virological response: 44% (32% and 70% for genotype 1 and non-genotype 1, respectively, p=0.04). Main side effects were anemia79%; leukopenia 68%; thrombocytopenia 64%; Blood transfusion 30%. **Conclusion:** Hepatitis C recurrence in liver transplant recipients occurred within a short period of time. The antiviral therapy was poorly tolerated and yielded a low sustained virological response rate. This data emphasized the need for new drugs, which are more effective and with a better safety profile, in the search for the eradication of the hepatitis C virus both before and after the liver transplantation.

Descriptors: Hepatitis C; Liver; Transplantation.

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Introduction

Cirrhosis due to hepatitis C virus (HCV) infection is the leading indication for liver transplantation in adults in the Western countries[1].However, the recurrence of HCV infection following the transplant is universal, and approximately 30% of these patients develop cirrhosis within five years[2].These data contradict the natural history of hepatitis C in non-transplant patients, in which about 10 to 20% of the patients will develop cirrhosis after many years of infection[3-4], thus indicating the severity of such infection in the liver transplant setting.

Recognizing characteristics both in the receptor and in the donor, which affected the natural history of HCV infection following liver transplant can have a great impact in the development of strategies aimed at minimizing the problem. Even though some clinical parameters have already been identified, there are not still any reliable means of recognizing which patients will have a rapid progression of the hepatic fibrosis after the transplant. Among the variables associated with the progression of the disease after the transplant, the following ones have already been mentioned: non-Caucasian ethnicity, high HCV viral load at the moment of the transplant, and cumulative dose of steroids[2].

The antiviral HCV treatment for patients who were subjected to liver transplant is, on the one hand, a priority, regardless of the state of the fibrosis[5]. On the other hand, it is a challenge considering its adverse events in this group of patients. Until recently, the standard therapy involving interferon alfa (IFN) or Pegylated interferon alfa (PegIFN) associated with ribavirin (RBV) was the only one recommended, but the success rates were reported as inferior to the ones registered in non-immunosuppressed patients, and a low tolerance was also identified[6].

Currently, the antiviral therapy for hepatitis C is going through important changes, and the new drugs available, such as the DAAs (direct-acting antivirals) may represent more safety, and efficiency scheduled therapy. These new drugs may be even administered to decompensated cirrhotic patients waiting for liver transplantation, although there are not widely available data for patients with Child-Pugh C cirrhosis[5]. Preliminary results from the DAAs therapy for liver transplanted patients are being published[7-11], but larger and more detailed studies that have already been concluded involving these patients are necessary before any of these new drugs are safely recommended for the different clinical situations that emerge after liver transplantation[12].

The aim of the present study was to describe the recurrence of HCV infection after liver transplantation, and the sustained virological response to interferon-based therapy in a cohort of liver transplant patients.

Patients and Methods

All medical records of HCV infected patients subjected to liver transplantation from 1998 to 2010 at the Hospital de Base, the University Hospital at the Medical School of Sao Jose do Rio Preto, Sao Paulo, were analyzed. Patients with at least one liver biopsy after the transplantation were included. HCV recurrence after liver transplantation was defined by the positivity of serum HCV RNA and histological evidence of hepatitis at liver biopsy. The first liver biopsy with histological parameters of viral damage was considered for diagnosis of time of hepatitis recurrence. The study excluded those patients without post-transplant liver biopsy or with medical records inconsistent or missing data.

Retrospective cohort study

The following clinical and laboratory variables were analyzed: demographic data of the receptor (age, gender) and the donor (age), laboratory data regarding the hepatic function, the HCV infection genotype), immunosuppression therapy, and time for hepatitis recurrence defined as the time from transplant to the date of histological recurrence of hepatitis C.

Histological analysis

All post-transplant biopsies were analyzed by a single experienced pathologist according to the Metavir classification criteria[13]. Protocol liver biopsies were performed yearly or for elevations in serum transaminase levels, and according to patient compliance.

Antiviral therapy

Patients subjected to antiviral therapy received weekly subcutaneous injections of IFN alfa or PegIFN alfa 2a or 2b both combined with daily doses of oral ribavirin. Treatment efficacy was defined as the presence of a sustained virological response (SVR), e.g., HCV RNA undetectable at post-treatment week 24. The antiviral therapy efficacy was analyzed under the intention-to-treat principle.

Statistical analysis

Descriptive analysis included absolute and relative frequencies for categorical variables, and means, medians, standard deviation, and variation for continuous variables. The normal distribution of the continuous variables was verified by analyzing the skewness and kurtosis and applying the Kolmogorov-Smirnov test of normality. The Student *t*-test was used to compare groups of continuous variables and the chi-square test or Fisher Exact test for categorical variables. Disease-free survival was defined as the time from the transplant to the date of histological recurrence of hepatitis C or the date of last liver biopsy. Survival analysis was performed using Kaplan-Meier estimator method. P value< 0.05 was considered significant. The statistical analysis was conducted through the IBM SPSS Statistics software for Windows, version 18 (IBM Corporation, NY, USA).

Ethical considerations

The study respected all ethics precepts specified by the Resolution 466/12 of the National Health Council. The study protocol was submitted to the local Ethics Committee (CEP/FAMERP) receiving authorization under protocol number 33815/2012.

Results

From the 147 liver transplanted patients with HCV during the period of the study, 80 were included in the study. Those without a liver biopsy after transplantation or whose records lacked information was excluded (67 patients). The clinical and demographic characteristics are in Table 1.

Table 1. Baseline characteristics of liver transplant recipients (n=80) with hepatitis C recurrence. São José do Rio Preto/SP, 1998 a 2000

Patient characteristics	
Age at transplantation (years)	50±10
Male gender	73%
White race	88%
Cirrhosis etiology	
HCV + alcohol	40.5%
HCV	32.4%
HCV + alcohol + HBV	20.3%
HCV + HBV	6.8%
Alcoholism pre-OLT (years)	23 ±10
Alcoholic abstinence pre-OLT (months)	24 (12-156)
HCVgenotype	
Genotype 1	67%
Genotype 2	10%
Genotype 3	23%
Donors age (years)	34.5 (9-67)
Pre-transplant diabetes	16%
Immunosuppression	
Prednisone	97%
Azathioprine	79%
Cyclosporine	71%
Tacrolimus	47%
Mycophenolate	34%
Rapamycin	33%

Continuous variables are expressed as mean ± standard deviation or median (range); categorical variables are expressed as proportions. HCV, hepatitis C virus; HBV, hepatitis B virus; OLT, orthotopic liver transplantation.

HCV recurrence after liver transplantation

Histological recurrence of hepatitis C occurred rapidly following liver transplantation (Table 2). There was histological evidence of hepatitis C in 40 of 56 patients (71%) subjected to liver biopsy within the first 6 months following liver transplantation.

Table 2. Histological recurrence* of hepatitis C following liver transplantation. São José do Rio Preto/SP, 1998 a 2000

Time	**N****
First 6 months after LT	40/56
Between 6 and 12 months after LT	5/5
Between 12 and 24 months after LT	10/14
Between 24 and 60 months after LT	1/2
Above 60 months after LT	1/2

*The first liver biopsy with histological parameters of viral damage was considered for diagnosis of time of hepatitis recurrence. **Number of patients with histological recurrence in relation to total number of liver biopsies performed in the period; the total number of performed liver biopsies excludes those from patients who had already histological recurrence in the previous period. LT, liver transplantation.

Disease-free survival analysis

The median follow-up period from liver transplantation to the date of histological recurrence of hepatitis C or the date of last liver biopsy was 9.7 months (the range was from 0.3 to 62 months). Disease-free survival curve is shown in figure 2. Median disease-free survival was 11.6 months.

Disease-free survival curve is shown in figure 1.

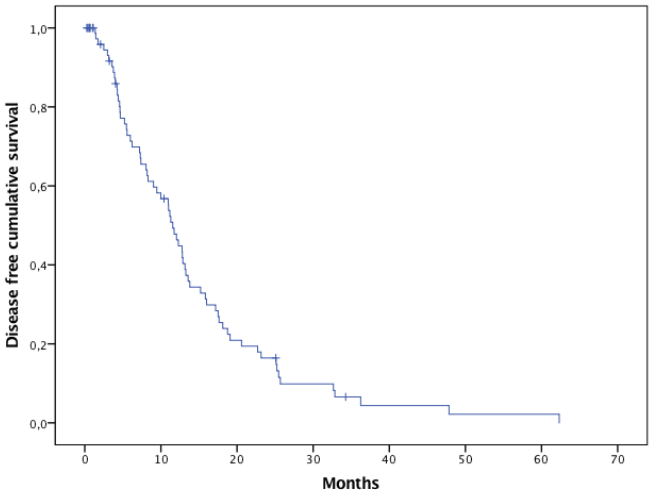

Figure 1. Disease-free survival according to Kaplan-Meier method. Disease-free survival was defined as the time from the transplant to the date of histological recurrence of hepatitis C or the date of last liver biopsy. Each drop in a probability curve indicates one or more events. Vertical lines indicate censored patients. São José do Rio Preto/SP, 1998 a 2000

Antiviral Treatment

Between 1998 and 2010, thirty-five patients were subjected to antiviral treatment with IFN+RBV (n = 12) or PegIFN+RBV (n = 23). The baseline characteristics of the patients submitted to antiviral treatment are in Table 3.

Table 3. Baseline characteristics of the patients submitted to antiviral treatment (n=35). São José do Rio Preto/SP, 1998 a 2000

Patient characteristics	
Age (years)	47±11
Male gender	27 (77%)
HCV Genotype	
Genotype 1	22 (67%)
Genotype 2	4 (12%)
Genotype 3	7 (21%)

Continuous variables are expressed as mean ± standard deviation; categorical variables are expressed as number (proportions). HCV, hepatitis C virus.

The global SVR rate was 44%. Cytopenia was the main side effect: anemia, 79%; leukopenia, 68%; thrombocytopenia, 64%. Blood transfusions were necessary in 30% of the patients. Comparative analyses between SVR group and non-responders group to antiviral therapy are in Table 4.

Table 4. Analysis of factors according to the type of treatment response. São José do Rio Preto/SP, 1998 a 2000

Patient characteristics	SVR	NR	P
Age (years)	43 ± 11	50 ± 10	0.06
Gender			
Male	12 (50%)	12 (50%)	0.41
Female	2 (25%)	6 (75%)	
HCV Genotype			
HCV genotype 1	7 (32%)	15 (68%)	0.04
HCV non-genotype 1	7 (70%)	3 (30%)	
IFN-containing regimens			
IFN + RBV	4 (36%)	7 (64%)	0.54
PegIFN + RBV	10 (48%)	11 (52%)	

Continuous variables are expressed as mean ± standard deviation; categorical variables are expressed as number (proportions). SVR, sustained virological responder group; NR, non-responder group; HCV, hepatitis C virus; IFN, interferon alfa; RBV, ribavirin; PegIFN, pegylated interferon alfa 2a.

Discussion

In this study, the HCV hepatitis recurrence occurred shortly after liver transplantation. It has been shown in the literature HCV reinfection of the liver transplant and hepatitis in 50% of the patients after one year, and 100% after five years of follow-up[2]. In accordance with these data, it was observed in the present study hepatitis recurrence about twelve-month post transplantation for half of the patients. The liver biopsies were indicated yearly or for elevations in serum transaminase levels and according to patient compliance; it is worth mentioning at times some patients did not agree with liver biopsy, or in some instances, it was impossible due to comorbid conditions. However, it is important to note the rigorous histology analysis performed by a single experienced pathologist allowed recurrence of hepatitis C to be diagnosed when only histological criteria of viral damage were present, excluding those with histological findings to other situations such as drug-induced hepatitis or graft rejection.

The natural history of cirrhosis caused by hepatitis C after liver transplant is unknown. An important study[14] tried to determine predictive factors for clinical decompensation, retransplantation, and mortality rates. All the patients were infected by HCV genotype 1b. The variables included were: histological activity rates after the transplant, hepatic function tests, age, gender, and maintenance immunosuppression. The research has shown that, in case a retransplantation is being considered, it must be conducted very early, since a decompensation may occur. Clinical decompensation was defined as the occurrence of ascites with or without peripheral edema, hydrothorax, varicose veins bleeding, spontaneous bacterial peritonitis, or encephalopathy during the follow-up.

Studies on the evolution of cirrhosis in the graft agree upon the fact that the recurrence of HCV infection causes hepatic failure in a great amount of patients, and the progression period is shorter than in the non-immunosuppressed patients[15].

Several risk factors for development of recurrent chronic HCV after liver transplantationhavebeen discussed, including recipient and donor factors. Although the HCV genotype and the appearance of quasispecies were at times reported as relevant factors regarding the recurrence of HCV. The lack of sufficient sensibility and specificity of the viral factors does not allow them to be used to determine which patients should be subjected to liver transplant and which ones should be given a preventive antiviral therapy. This is also true for the variables regarding the receptor, including age, gender, and ethnicity[15]. Among donor factors, it is important to emphasize that several studies confirm the relation between the advanced donor age with a earlier and more severe histological progression of the HCV recurrence and a decrease in survival of recipients[16].Even though the median age of liver donor in the present study was 34.5 years, there was a considerable variability with the maximum age being 67 years.

The treatment in the immediate postoperative period is tolerated, but the efficiency is normally unsatisfactory, according to the literature. Preventive therapy refers to the antiviral therapy that begins within two to eight weeks after the transplant, when the viral load is low and there are no histological damages, and it is not adopted in the routine practice. The factors that contribute to low response rates among the receptors of liver transplant include: bone marrow suppression by IFN, when used in combination with immunosuppression drugs, and low tolerance to ribavirin[17]. Other factors associated with low responses are: genotype 1, absence of premature virological response, male gender, high basal viral load and resistance to insulin[17]. In the present study, antiviral therapy yielded a low SVR rate; data also noticed a considerable difference in the SVR rates when HCV genotypes 1 and non-genotype 1 was compared, which confirmed the data provided by the literature[18]. In relation to age, there was a trend towards higher rates of SVR in younger patients but this difference did not reach statistical significance; the comparative analysis of SVR according to gender did not show any relevant differences.

Side effects were frequent in this study. The most important side effect was cytopenia and approximately one-third of patients required blood transfusion. Similar Results were reported by other groups[19-21]. In a revision about treatment[21], almost a third of the patients had their treatment interrupted due to this side effect, and the others needed a dose reduction to increase the tolerance.

Some authors defend[17] that the antiviral therapy must be offered to all patients as soon as histological evidence of HCV relapses is detected. Another important consideration is that, in case a re-transplantation is being discussed, a prophylactic antiviral therapy would be the most effective measure in order to reduce the progression of the disease after the transplantation, and this option is not available in clinical practice.

The new antiviral treatment for HCV was available for some countries[5,6]and it is very likely to increase the tolerance, and the efficiency for patients subjected to liver transplant as well[22-24]. More evidence produced by real-life studies is still to be published involving a large number of patients in this specific group and is being widely anticipated[25]. Certainly soon this treatment will be started earlier for these patients due to better tolerance and

efficacy. It is also possible to anticipate this therapeutic measure will potentially prevent the progression to cirrhosis due to HCV recurrence after liver transplantation and subsequently increase survival for this group of patients.

Conclusion

Hepatitis C recurrence in liver transplant recipients occurred within a short period of time. The antiviral therapy was poorly tolerated and yielded a low SVR rate. This data emphasized the need for new drugs, more effective and with a better safety profile, in thesearch for the eradication of the HCV both before and after the liver transplantation.

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