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Acute Hepatitis C in Brazil: Results of a National Survey

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The incidence of acute hepatitis C has decreased in the world. However, new cases are still reported. The objective of this study was to obtain data of acute hepatitis C in Brazil and to identify risk factors of transmission, diagnostic criteria, clinical presentation, evolution, and treatment. A questionnaire was sent to all members of the Brazilian Society of Hepatology. Sixteen centers participated with a total of 170 cases between 2000 and 2008. Among them, 37 had chronic renal failure on hemodialysis and were evaluated separately. The main diagnostic criterion in non-uremic patients was ALT (alanine aminotransferase) elevation associated with risk factors. In patients with chronic renal failure, anti-hepatitis C virus (HCV) seroconversion was the most frequent criterion. Among the 133 non-uremic patients the main risk factors were hospital procedures, whereas in hemodialysis patients, dialysis was the single risk factor in 95% of the cases. Jaundice was more frequent in non-uremic patients (82% vs. 13%; $P < 0.001$) and ALT levels were higher in these individuals ($P < 0.001$). Spontaneous clearance was more frequent in non-uremic patients (51% vs. 3%; $P < 0.001$). Sixty-five patients were treated: 39 non-uremic patients and 26 on dialysis. Sustained virological response rates were 60% for non-uremic and 58% for uremic patients ($P = 0.98$). There was no association of these rates with the study variables. These findings show that cases of acute hepatitis C are still occurring and have been related predominantly to hospital procedures. Measures to prevent nosocomial transmission should be adopted rigorously and followed to minimize this important source of infection observed in this survey. ***J. Med. Virol. 83:1738–1743, 2011.***

KEY WORDS: acute hepatitis C; Brazil; epidemiology; HCV; risk factors

INTRODUCTION

The incidence of new cases of hepatitis C virus (HCV) infection has declined markedly over the last few years since transfusions of blood and blood products are tested for markers of infection with HCV in most countries. This is demonstrated by the annual

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rates of new infections with HCV notified in the United States, which decreased from 2.5/100,000 inhabitants at the beginning of the 1990s to 0.3/100,000 inhabitants in 2006 [Wasley et al., 2008]. Despite these data, new infections continue to occur by other transmission routes.

Geographic differences between risk factors have been reported in studies on acute hepatitis C. Whereas unsafe injection practices by illicit drug users are the main routes of transmission of hepatitis C in the United States and most industrialized countries [Kamal, 2008; Wasley et al., 2008], invasive procedures performed at health services centers have become the most important factor in other regions of the world [Irving et al., 2008; Kamal, 2008; Martínez-Bauer et al., 2008; Santantonio et al., 2008; Sharaf Eldin et al., 2008]. Other routes of transmission reported less frequently are occupational exposure and uncommonly perinatal transmission and sexual contact with virus carriers [Irving et al., 2008; Cox et al., 2009]. Differences in socioeconomic conditions and in the prevalence rates of infection between different regions may explain the divergence in transmission routes [Kamal, 2008].

Most patients infected with HCV become chronic carriers [Heller and Rehermann, 2005], a reason which justifies that patients should be submitted to specific treatment during this phase. Doubts remain regarding the criteria for indication, treatment regimens to be used, and the ideal time for the initiation of treatment. Numerous studies regarding the treatment of acute hepatitis C with conventional or pegylated interferon have been published. Despite the differences in terms of beginning treatment, doses and duration of treatment, most of these studies report sustained virological response rates ranging from 45 to 100% [Alberti et al., 2002; Licata et al., 2003; Kamal et al., 2006a; Kamal et al., 2006b; Wiegand et al., 2006].

No information is available regarding the characteristics of acute HCV infection in Brazil. Therefore, a national survey coordinated by the Brazilian Society of Hepatology was conducted in order to gather information on cases of acute hepatitis C, including mechanisms of transmission, diagnosis, progression, and treatment.

PATIENTS AND METHODS

In May 2008, a letter was sent to all members of Brazilian Society of Hepatology, in which they were invited to participate in a national survey and asked to complete a standardized questionnaire for each case diagnosed as acute hepatitis C. The questionnaire included the following variables: Demographic data, diagnostic criteria, probable mechanisms of transmission, clinical manifestations, alanine aminotransferase (ALT) levels at the time of diagnosis, virus genotype, progression, and time of follow-up to spontaneous viral clearance. In cases submitted to treatment, the time of beginning treatment, therapeutic regimen, and treatment response were evaluated.

The following diagnostic criteria were defined: 1) documented anti-HCV seroconversion over the last 6 months; 2) ALT elevation ($>10\times$ upper normal limit) associated with negative anti-HCV antibodies and positive HCV RNA; 3) ALT elevation ($>10\times$ upper normal limit) associated with positive anti-HCV antibodies and HCV RNA at the time of diagnosis and presence of risk factors over the last 6 months.

Risk factors were the use of parenteral drugs, occupational exposure, acupuncture, piercing, dental treatment, use of razors in a barbershop, sexual transmission (sexual partner infected with HCV or multiple sexual partners), hospital procedures (hospital admission, surgery, hemodialysis, organ transplant, procedure with venous access, and endoscopy), and transfusion of blood and blood derivatives. These factors were considered when they occurred during the last 6 months prior to the diagnosis. Other possible causes of acute hepatitis (hepatitis A, B, drug toxicity, alcohol abuse) should have been investigated and ruled out. The study was approved by the Ethical Committee of The Federal University of Maranhão Hospital.

STATISTICAL ANALYSIS

Numerical variables are reported as the mean and standard deviation or as the median and range. Categorical variables are expressed as absolute numbers and proportions. Differences between numerical variables were evaluated by the Student *t*-test and differences between categorical variables by the Chi-square test. The SPSS program, version 14, was used for statistical analysis.

RESULTS

Sixteen centers of the country participated in the survey and 170 cases followed up between 2000 and 2008 were reported. Thirty-seven (21%) of these cases were patients with chronic renal failure treated by dialysis. Since the proportion of these cases was high and most basic characteristics of these patients differed from those described for the group as a whole, they were analyzed separately when indicated.

Differences in the general characteristics of the patients according to the presence or absence of renal failure are shown in Table I.

Determination of the viral genotype was possible in 97 patients, including 76 non-uremic patients and 21 on dialysis. Genotype 1 was the most prevalent in the two groups: 61 (80%) non-uremic patients and 12 (57%) patients with renal disease.

The main criterion for the diagnosis of acute hepatitis C among non-uremic patients was ALT elevation ($>10\times$ upper normal limit) associated with positive anti-HCV antibodies and HCV-RNA at the time of diagnosis and presence of a risk factor during the

TABLE I. Characteristics of the 170 Patients With Acute Hepatitis C (Brazil, 2000–2008)

	Non-uremic (n = 133)	Uremic (n = 37)	*P*
Gender			
Female	85 (64%)	17 (46%)	0.04
Male	48 (36%)	20 (54%)	
Age (years)*	42 (13–80)	47 (25–67)	0.14
Clinical symptoms	118 (89%)	6 (16%)	<0.001
Jaundice	108 (82%)	5 (13%)	<0.001
ALT (×UNL)	28 (1–113)	8 (1–47)	<0.001

×UNL: Times upper normal limit.
*Median (range).

TABLE III. Probable Risk Factor for Infection With HCV in 170 Cases of Acute Hepatitis C (Brazil, 2000–2008)*

Surgery	48 (28%)
Hemodialysis	37 (22%)
Sexual contact	28 (16%)
Hospital admission	17 (8.5%)
Occupational accident	7 (4%)
Use of injectable illicit drugs	3 (2%)
Dental treatment	4 (2%)
Blood transfusion	9 (2%)
Organ transplant	3 (2%)
Endoscopy of digestive tract	2 (1%)
Others	8 (4%)
Unknown	16 (10%)

*Fourteen patients presented more than one risk factor.

last 6 months. In contrast, documented anti-HCV seroconversion was the main criterion among dialysis patients. Two patients under hemodialysis were anti-HCV negative after the diagnosis of acute hepatitis despite the detection of HCV RNA (Table II).

Among the 133 non-uremic patients, a single risk factor could be attributed to 105 (79%) patients, 12 (9%) presented more than one risk factor, and 16 (12%) presented no identifiable risk factor. Hemodialysis was the only risk factor identified in 35 (95%) of the 37 patients with renal failure and two patients presented hospital admission and elective surgery as risk factors in addition to dialysis. When analyzing the group as a whole, the main risk factors were hospital procedures even among patients who presented with more than one identifiable risk factor (Table III).

Among the 133 non-uremic patients, spontaneous resolution of the infection was observed in 68 (51%) the infection became chronic in 57 (42%), and 8 (7%) patients were lost to follow-up. Among uremic patients, spontaneous viral clearance was observed in only one case.

The median time from the diagnosis of acute hepatitis C infection to viral clearance was 13 weeks (1–146 weeks). Factors associated with viral clearance are shown in Table IV.

Sixty-five (70%) of the 93 patients who did not clear the virus were treated. Of these, 39 were non-uremic patients and 26 were patients on dialysis. Among the 65 treated patients (with or without renal failure), the median time from diagnosis to the onset of treatment was 24 weeks (2–135 weeks). The therapeutic regimens used and the duration of treatment in non-uremic and uremic patients are shown in Tables V and VI.

At the end of the survey, the 6-month final outcomes after the end of treatment were available for 56/65 patients. Thirty-two patients were non-uremic and 24 had renal failure. A sustained virological response was observed for 19 (60%) of the 32 non-uremic patients and for 14 (58%) of the 24 uremic patients, with no difference in these rates ($P = 0.98$).

No association was observed between sustained virological response and gender ($P = 0.49$), age ($P = 0.45$), HCV genotype ($P = 0.95$), type of interferon used: Conventional or pegylated ($P = 0.17$), treatment duration in weeks ($P = 0.46$), or time from diagnosis to the start of treatment ($P = 0.41$).

TABLE II. Diagnostic Criteria Applied to the 170 Cases of Acute Hepatitis C (Brazil, 2000–2008)

Case definition	Non-uremic (n = 133)	Uremic (n = 37)	*P*
ALT >10× UNL, anti-HCV and HCV-RNA positive, risk factor during the last 6 months	86 (64%)	3 (8%)	
Documented anti-HCV seroconversion	47 (36%)	32 (87%)	
ALT >10× UNL, anti-HCV negative, and HCV-RNA positive	0 (0%)	2 (5%)	<0.001

× UNL: Times upper normal limit.

DISCUSSION

This national survey permitted the analysis of an expressive number of cases of acute HCV infection. Among the 170 cases studied, a significant proportion corresponded to patients with renal failure under hemodialysis (21%). This group of patients was evaluated separately because of their distinct clinical presentation, evolution, and treatment. Among the

TABLE IV. Factors Associated With Spontaneous Viral Clearance in Acute Hepatitis C (n = 162) (Brazil, 2002–2008)

	Clearance (n = 69)	Chronic infection (n = 93)	*P*
Female gender, n (%)	44 (63%)	55 (59%)	0.34
Symptomatic, n (%)	67 (97%)	49 (52%)	<0.0001
Jaundice, n (%)	63 (91%)	42 (45%)	<0.0001
Age (years)*	43 ± 12	44 ± 13	0.50
ALT (×UNL)	34 ± 22	20 ± 19	<0.0001
Patients on dialysis, n (%)	1 (3%)	36 (38%)	<0.0001

×UNL: Times upper normal limit.
*Mean ± standard deviation.

TABLE V. Therapeutic Regimen and Duration of Treatment of Acute Hepatitis C in Non-Uremic Patients (n = 39)

Conventional interferon alone	13 (33%)
Conventional interferon + ribavirin	15 (38%)
Pegylated interferon alone	2 (6%)
Pegylated interferon + ribavirin	9 (23%)
Treatment duration (weeks), median (range)	24 (16–72)

133 non-uremic patients, the diagnosis was established in most cases based on the presence of elevated ALT (>10× upper normal level) and the detection of anti-HCV antibodies and HCV RNA at the time of clinical presentation, associated with the presence of a risk factor during the last 6 months. The second most frequent criterion was documented anti-HCV seroconversion. These diagnostic criteria were the same used in most published series [Moreira et al., 2003; Kamal, 2008; Martínez-Bauer et al., 2008; Santantonio et al., 2008].

On the other hand, the main diagnostic criterion in patients with renal failure was documented anti-HCV seroconversion as expected, since screening for this infection is performed routinely in this population. Two of these patients on dialysis were persistently negative for anti-HCV, although they were positive for HCV RNA during the episode of acute hepatitis when other causes were excluded. Discordant results between serological assays and molecular biology tests used for the detection of HCV infection in patients with renal failure on dialysis have been demonstrated [Moreira et al., 2003; Kalantar-Zadeh et al., 2005]. The inability of some of these patients to produce antibodies has been attributed to immunological deficiency [Kalantar-Zadeh et al., 2005; Hussein et al., 2007].

With respect to the mechanism of transmission, the presence of a risk factor 6 months prior to the diagnosis was identified in 154 (90%) patients. A single risk factor was present in 140/154 patients (91%) and associated mainly with hospital procedures such as surgeries, hemodialysis, and hospital admission. Hemodialysis is a well-documented risk factor for HCV infection [Fabrizi et al., 2008] and this infection was shown to be related mainly to nosocomial transmission rather than blood transfusions. Other studies also reported nosocomial transmission in non-uremic patients. Published Italian and Spanish studies involving a large number of cases showed that hospital admission was responsible for 47 and 70% of cases of acute hepatitis C, respectively [Santantonio et al., 2006; Martínez-Bauer et al., 2008]. This fact, which was also observed in the present study, indicates the need for measures to prevent nosocomial transmission of this infection.

TABLE VI. Therapeutic Regimen and Duration of Treatment of Acute Hepatitis C in Patients With Chronic Renal Failure on Dialysis (n = 26)

Conventional interferon alone	24 (92%)
Pegylated interferon alone	2 (8%)
Treatment duration (weeks), median (range)	48 (24–48)

Another risk factor identified was possible sexual transmission observed in 16% of the patients and defined in this study as sexual contact with partner infected with HCV or with multiple partners over the last 6 months. This rate might be overestimated in view of the difficulties in characterizing this route of transmission when epidemiological questionnaires are used. In fact, sexual transmission of HCV is a matter of controversy, although this mechanism has been reported to be important by some investigators, especially in the United States, where this route of transmission accounted for 20–35% of cases of acute hepatitis C between 2000 and 2006 [Wasley et al., 2008].

The use of injectable illicit drugs as a risk factor was rare in the present study, corresponding to only 2% of cases, a percentage much lower than those reported in most series [Santantonio et al., 2006; Irving et al., 2008; Cox et al., 2009]. This finding might indicate that injectable drug use is not a frequent mechanism of transmission of HCV in Brazil, or that this rate is underestimated due to a purposely negative response among those who actually use injectable drugs.

With respect to clinical presentation, most of non-uremic patients presented symptoms and the icteric form of hepatitis. These findings are similar to those reported in other studies on acute infection with HCV [Santantonio et al., 2006; Kamal, 2008]. In view of inevitable selection bias, since the identification of anicteric forms is only possible by prospective screening of cases exposed to risk factors which, in fact, was observed among uremic patients on dialysis.

Spontaneous viral clearance showed a frequency of 50% among non-uremic patients and occurred within a median period of 13 weeks after diagnosis. These findings are similar to those reported in the main series published in the literature [Lechner et al., 2000; Heller and Rehermann, 2005; Ishii & Koziel, 2008]. This high cure rate may reflect the fact that most of these patients were symptomatic, indicating a better immune response to infection [Gerlach et al., 2003; Micaleff et al., 2006]. Analysis of factors associated with spontaneous viral clearance showed that the presence of symptoms, jaundice, and elevated ALT levels was associated with a higher rate of viral clearance. Taken together, these factors suggest that a vigorous initial immune response is important for the spontaneous clearance of infection. For the same reason, the clearance rate was significantly lower among uremic patients, with viral clearance being observed in only one case, in agreement with the literature [Okuda et al., 1998].

Most of the patients who progressed to chronic infection (70%) were treated. Since a large number of

centers participated in this survey, various treatment regimens were reported, including conventional interferon or pegylated interferon alone or in combination with ribavirin. The duration of treatment ranged from 16 to 72 weeks, with a median of 24 weeks for non-uremic patients and of 48 weeks for patients with renal failure. The sustained virological response rate was 60% for non-uremic patients and 58% for uremic patients. That rate obtained for non-uremic patients is below those reported in most studies [Jaeckel et al., 2001; Alberti et al., 2002; Kamal et al., 2004; Santantonio et al., 2005; Wiegand et al., 2006; Kamal et al., 2006a; Kamal et al., 2006b; Calleri et al., 2007]. This lower rate might be explained by the longer timespan from diagnosis to onset of treatment than that recommended currently, with a median of 24 weeks in this group of patients. The rate observed for uremic patients is compatible with the rates reported in the literature [Al-Harbi et al., 2005; Engel et al., 2007; Rocha et al., 2007].

No factors associated with a sustained virological response were identified. The heterogeneity of treatment, including small groups for each regimen, possibility compromised the identification of predictive factors of response in this sample. In conclusion, acute infection with HCV continues to occur in Brazil. Hospital procedures were the most frequent identified factors of transmission. Risk factors described traditionally for industrialized countries, such as injectable drug use, were rare. With respect to therapeutic management, no standard therapeutic regimen used by all services could be identified. In addition, the beginning time of treatment was longer than that recommended currently, a fact that might have been responsible for the lower sustained virological response rate observed when compared to the rates reported in the literature. These findings indicate that measures to prevent nosocomial transmission should be implemented and followed in order to minimize this important route of transmission in Brazil. Late onset of treatment should be avoided to optimize cure rates and to reduce the possible progression to chronic forms of infection.

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