Assessment of the treatment of chronic hepatitis C in the state of Mato Grosso, central Brazil

Francisco Kennedy Scofoni Faleiros de Azevedo[1], Cassius Clay Scofoni Faleiros de Azevedo[2], Francisco José Dutra Souto[1]/+

[1]Hospital Universitário Júlio Muller, Universidade Federal de Mato Grosso, Rua Luis Philippe Pereira Leite s/n, 78048-902 Cuiabá, MT, Brasil
[2]Pronto Socorro Municipal de Várzea Grande, Várzea Grande, MT, Brasil

In Brazil, the treatment of hepatitis C virus (HCV) infection is funded by the national public health system (SUS). To evaluate treatment results in the state of Mato Grosso, central Brazil, we have consulted the files of the office of the State Department of Health responsible for supplying such medications. We obtained information on 232 treatments of 201 patients who underwent treatment in or prior to 2008. The study was conducted by reviewing medical records, making telephone calls and interviewing the assistant physicians. Thirty-nine patients (19.4%) had cirrhosis and HCV genotype 1 predominated (64.3%). Excluding patients with comorbidities or treatment without ribavirin we analysed 175 treatments (sustained virologic response occurred in 32.6% of cases). Twenty-six of these 175 were retreatments and the sustained virological response (SVR) rate among them was 30.8%; the SVR rate was 32.9% among those receiving treatment for the first time. The SVR rate of genotype 1 patients was 27.8%, whereas it was 37.5% in non-1 genotype patients. The adjusted multivariate analysis showed association of SVR with the absence of cirrhosis [odds ratio (OR): 7.7; confidence interval (CI) 95%: 2.5, 33.3], the use of pegylated interferon (OR: 5.8; CI 95%: 1.5, 21.4), non-1 genotype (OR: 5.3; CI 95%: 1.7, 16.7) and uninterrupted treatment (OR: 9.0; CI 95%: 3.3, 45.4). The SVR rates were similar to those found in other Brazilian studies about HCV, but lower than those found in national and international clinical trials. These data suggest that the treatments of chronic hepatitis C that are made available by SUS does not, under normal conditions, work as well as the original controlled studies indicated.

Key words: chronic hepatitis C - treatment - pegylated interferon - ribavirin - conventional interferon - sustained virological response

The hepatitis C virus (HCV) is one of the main causes of chronic hepatitis worldwide and is responsible for a large percentage of cases of cirrhosis and hepatocellular carcinoma as well as referrals for liver transplant (Kim 2002, Thomas & Seeff 2005, Ghany et al. 2009).

Starting in the 1990s, the treatment of chronic hepatitis C with medication was able to change the history of the disease, thus avoiding its complications (Ghany et al. 2009). The first medication used was [conventional interferon-α (IFN-α) (IFNc)], which was successful in fewer than 20% of cases (Davis et al. 1989). Later, the combination of IFNc with ribavirin (RBV) increased the chances of a sustained virological response (SVR), which denotes the absence of detectable HCV RNA in the plasma for at least six months after treatment is concluded in approximately 35-40% of cases (Poynard et al. 1998). In early 2000, the pegylation process allowed an increase in the half-life of IFN-α 2a and 2b (PEG-IFN) (Manns et al. 2001, Fried et al. 2002). Currently, close to half of all cases reach SVR when PEG is combined with RBV (Hadziyannis et al. 2004).

In North America and Europe, HCV is treated with PEG-IFN and RBV for six months (for genotypes 2 and 3) or for 12 months (for genotype 1). In Brazil, the Ministry of Health [through the national public health system (SUS)] provides these medications free of charge, but limits the prescription of PEG-IFN to genotype 1, supplying IFNc for the treatment of other genotypes (pursuant to Administrative Rule 34 of 28 September 2007). This practice is based on a multicentre clinical trial of one of the pegylated IFNs on the market (2b), which suggested that there was no statistically significant difference between PEG-IFN and IFNc combined with RBV for genotypes 2 and 3 (Manns et al. 2001).

It is possible to attain SVR using PEG-IFN and RBV in patients in whom previous therapy with IFNc and RBV for chronic hepatitis had failed. Sherman et al. (2006) demonstrated SVR in 43% of relapsing patients in whom RNA-HCV suppression was achieved during treatment, but who tested positive again after the medication was discontinued and in 32% of patients who did not respond to IFNc plus RBV.

Despite the evolution of treatment, there are still obstacles for its application on a large scale, such as the high cost of the recommended drugs and the high incidence of side effects. This treatment is contraindicated for patients with decompensated cirrhosis, thrombocytopenia or neutropenia, serious heart diseases or mental illnesses.

In the past few years, some studies have been published in the Brazilian medical literature describing the experiences of different healthcare service providers

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+ Corresponding author: fsouto@terra.com.br
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with the treatment of chronic hepatitis C in Brazil (Alves et al. 2003, Figueiredo-Mendes et al. 2003, Acras et al. 2004, Brandão et al. 2006, Gonçales et al. 2006, 2010, Parise et al. 2006, Silva et al. 2007, Vigani et al. 2008, Almeida et al. 2009). These reports include experiences in the South and Southeast Regions of the country. The purpose of the present study is to describe and analyse the results of the treatment of chronic hepatitis C in the state of Mato Grosso (MT), as there are no known reports of this type for the Central-West Region of Brazil.

PATIENTS, MATERIALS AND METHODS

Upon reviewing the lists of treatment authorised by the Farmácia de Alto Custo (FAC), the government-run pharmacy for the distribution of high-cost drugs of the Mato Grosso State Department of Health (SSEMT), we identified a total of 268 patients treated between 2002-2008. As there is no public health unit specifically designated to manage IFN injections in MT, these medications are delivered directly to the patients, who are then personally responsible for administering the injections. Consequently, there are no official records in FAC files indicating whether these treatments were completed or successful. To gather patient information, we sought the help of the assisting physicians who had ordered the medications. We asked the permission of these physicians to access the medical records of their patients at the respective clinics and healthcare centres; we also obtained permission from the directors of each medical institution.

We sought information regarding the demographics of the patients, the characteristics of the cases, such as the genotype and the kind of IFN-α prescribed and the outcomes of the treatments. Whenever available, the results of the liver biopsies were expressed using the METAVIR score for fibrosis and inflammatory activity (Bedossa & Poynard 1996).

The outcome of interest (the SVR) was defined as non-detection of HCV RNA for at least six months after the conclusion of treatment. Patients who stopped the treatment before the recommended schedule due to side effects, intolerance or problems caused by periods of irregularity of drug delivery from the public health service were classified as "having interrupted the treatment".

The data obtained were stored using the software EpiInfo 6.04d (Centers for Disease Control and Prevention, Atlanta, USA). Appropriate statistical tests were performed to compare continuous and categorical variables, with respective dispersion and a confidence interval (CI) of 95%, using the same software. A logistic regression model was created to analyse the association of SVR with the variables related to it according to univariate analysis. Classical variables were also included in the model, even if they were not associated with SVR in univariate analysis. For this analysis, a stepwise method was used in Stata 8.2 (Stata Corporation, College Station, Texas, USA, 2005).

The ethical aspects of the project were analysed and approved on 15 April 2009, by the Research Ethical Committee of the University Hospital Julio Muller of the Federal University of Mato Grosso under protocol 599/08.

RESULTS

Of the 268 individuals registered at the FAC who requested medication for the treatment of chronic hepatitis C from 2002-2008 we obtained information on 201 patients corresponding to 232 initial treatments and 31 retreatments. We were only able to recover the outcomes of 197 treatments. The majority of these treatments (52.6%) took place in public health institutions.

Of the 201 individuals, 145 (72.1%) were male (Table I). The average age of the 201 patients at the beginning of treatment was 48 years old (46 for male patients and 50 for female patients). The average age of the 31 patients who underwent retreatment was 51. The majority of the patients were Caucasians, but there were a large proportion of individuals with a mix of European, African and Native South American ancestries. The difficulty of classifying the ethnicities of participants prevented any outcomes analysis that included ethnicity as a variable.

We were able to recover information on the HCV genotypes of 157 patients (77.6%). Genotype 1 was responsible for the largest number of cases (101, 64.3%), followed by genotype 3 (46 cases, 29.3%). It was not possible to recover information on the dosage of RBV used in a large number of the patients. Most of the patients received 1 g daily, but data on dosage reduction was scarce. Therefore, we were unable to analyse the effects of this important variable on the final result of the treatment.

Of the 197 treatments with recovered results, SVR was present in 30.9% of them (CI 95% = 24.6-38%). Be-

TABLE I

Characteristics of the 201 patients who underwent treatment for chronic hepatitis C in the state of Mato Grosso, Brazil, from 2002-2008, with medication supplied by public health

	Total n (%)
Total	201
Gender	
Male	145 (72.1)
Female	56 (27.9)
Age (average, extremes)	48 (16-68)
Initial treatments	201 (86.6)
Retreatments	31 (13.4)
Know genotype	157 (78.1)
1	101 (64.3)
2	9 (5.7)
3	46 (29.3)
5	1 (0.7)
Unknown	44 (21.9)
Cirrhosis	39 (19.4)
Fibrosis stage[a]	71 (35.3)
0-2	24 (50.7)
3-4	47 (49.3)

a: classification according to Metavir (Bedossa & Poynard 1996).

cause some of these patients had not received a therapeutic scheme with RBV due to contraindication (renal failure and dialysis treatment) and because some of the patients were co-infected with HIV, we did not include these patients to better compare the results with those of other reports and trials. Therefore, 149 patients (26 of whom were retreatments) who received 175 treatments with IFN-α (IFNc or PEG-IFN) and RBV were included in the study. The global SVR in this group was 32.6%. For patients who received PEG-IFN the SVR was 35.3% and for patients who received IFNc, the SVR was 27.1% (p = 0.353). The SVR rates were slightly higher for the patients undergoing initial treatments (32.9%) than for those undergoing retreatment (30.8%, p = 0.831) and they were also higher in patients infected by a non-1 genotype (37.5%) than in those infected by genotype 1 (27.8%, p = 0.295). Regarding only the patients infected by non-1 genotypes, there was a better response to the use of the combination of PEG-IFN and RBV compared to the combination of IFNc and RBV (52.9% vs. 20.9%, p = 0.034) (Table II). Eighty-seven (75%) of 116 treatments with PEG-IFN were performed with PEG-IFN-α 2a. Because there were few treatments (25%) with PEG-IFN-α 2b, comparison between the products was not possible.

Thirty-four (23.8%) of 143 patients had cirrhosis (data unavailable for 6 patients) at the beginning of the treatment and they were diagnosed through histopathology or through clinic and laboratory data. They corresponded to 46 treatments and retreatments and 15.2% had SVRs.

Multivariate analysis showed that infection by non-1 genotypes, the use of therapeutic schedules employing PEG-IFN, non-interruption of treatment and the absence of cirrhosis were independent factors associated with SVR (Table III). The outcome was not influenced by the patient's gender or age, whether the patient was treated at public or private healthcare facilities, or whether the patient was undergoing first treatment or retreatment.

TABLE II

Results of the 175 treatments with ribavirin (RBV) carried out in patients without human immunodeficiency virus infection or chronic renal failure, regarding type of interferon used, whether it was the initial treatment or retreatment, and genotype

	Total n	SVR n (%)	p value
Total	175	57 (32.6)	-
Initial treatments	149	49 (32.9)	-
Retreatments	26	8 (30.8)	0.831
Genotype 1	90	25 (27.8)	-
Genotype other than 1	56	21 (37.5)	0.218
Unidentified genotype	29	11 (37.9)	0.300
All treatments of cirrhotic patients	46	7 (15.2)	-
All treatments of non-cirrhotic patients	123	49 (39.8)	0.004
Therapy regimen with PEG-IFN and RBV	116	41 (35.3)	-
Therapy regimen with IFNc and RBV	59	16 (27.1)	0.272
Initial treatments with PEG-IFN and RBV	93	33 (35.5)	-
Initial treatments with IFNc and RBV	56	16 (28.6)	0.384
Retreatments with PEG-IFN and RBV	23	8 (34.8)	-
Retreatments with IFNc and RBV	3	0 (0)	0.219[a]
Genotype 1 (n = 90)			
Treatments with PEG-IFN and RBV	78	23 (29.4)	-
Treatments with IFNc and RBV	12	2 (16.7)	0.355
Initial treatments	77	22 (28.6)	-
Using PEG-IFN and RBV	66	20 (30.3)	-
Using IFNc and RBV	11	2 (22.2)	0.497[a]
Retreatments	13	3 (23.1)	-
Using PEG-IFN and RBV	12	3 (25)	-
Non-1 genotype (n = 56)			
Treatments with PEG-IFN and RBV	17	9 (52.9)	-
Treatments with IFNc and RBV	39	8 (20.9)	0.034
Initial treatments	44	17 (38.6)	-
Using PEG-IFN and RBV	7	5 (71.4)	-
Using IFNc and RBV	37	12 (32.4)	0.089[a]
Retreatments	12	4 (33.3)	-
Using PEG-IFN and RBV	10	4 (40)	-

a: Fisher exact test; IFNc: conventional interferon-α (IFNc); PEG-IFN: pegylated IFN; SVR: sustained virological response.

DISCUSSION

This is the first study that analyses the efficacy of the treatment of chronic hepatitis C in MT. Similar studies have been conducted in the country's South and Southeast Regions, but this is the first one conducted in the Central-West Region. The results of these studies are shown in Table IV. Also included in Table IV are results from Phase 3 approval studies of PEG-INF to characterise the differences between experimental and post-market studies.

Because the drugs that treat hepatitis C are very expensive, almost all patients, even those who receive treatment at private hospitals, access these drugs through the SUS. Therefore, we assume that the data presented in this study are representative of hepatitis C therapy in MT. In the present study, treatments administered in private hospitals and clinics did not achieve better SVR than those administered in public health institutions.

It was not possible to obtain information on 67 (25%) of the 268 patients listed at the FAC-SSEMT as receiving these medications between 2002-2008, despite our attempts to contact via telephone the institutions in which they were treated, their physicians or even the patients themselves. In many cases, the information on these cases was lost due to changes of address or phone numbers, but it also demonstrates the unreliability of the medical records kept in healthcare institutions and hospitals in MT.

Some of the characteristics of the sample, such as age and the preponderance of both male subjects and genotype 1, demonstrate that the present sample is similar to those from other series of clinical cases, which corroborates the results found and reduces the chance of a selection bias resulting from the loss of data (Zeuzem et al. 2000, Alves et al. 2003, Figueiredo-Mendes et al. 2003, Gonçales et al. 2006, Parise et al. 2006, Silva et al. 2007, Vigani et al. 2008, Almeida et al. 2009, McHutchison et al. 2009). Regarding genotype in particular, previous studies had already demonstrated that genotype 1 is predominant in MT, as it is in most of Brazil (Campiotto et al. 2005).

For the analysis of SVR rates, we considered 175 treatments that included RBV in the therapeutic regimen, excluding patients with HIV or renal failure, to make the population studied resemble those in similar studies. The SVR rate of 32.6% was lower than that observed in prospective studies, which report an SVR of approximately 50% (Manns et al. 2001, Fried et al. 2002, Brandão et al. 2006, Gonçales et al. 2006, Silva et al. 2007), but similar to that observed in several retrospective studies in the country (Alves et al. 2003, Figueiredo-Mendes et al. 2003, Acras et al. 2004, Vigani et al. 2008, Almeida et al. 2009). These numbers suggest that in real-life conditions, the results obtained by the Brazilian healthcare services are not comparable to the results obtained in controlled trials, a fact that should be addressed by the country's public health authorities.

Cirrhosis was present in 19.4% of the 201 patients. Other national and international studies describe an incidence of cirrhosis ranging from 12-27% (Manns et al. 2001, Fried et al. 2002, Alves et al. 2003, Figueiredo-Mendes et al. 2003, Gonçales et al. 2006, Parise et al.

TABLE III

Multivariate analysis of the influencing factors on the sustained virological response (SVR) in the treatment of hepatitis C patients in the state of Mato Grosso, Brazil, considering only therapy regimens using ribavirin (RBV) and patients not infected with human immunodeficiency virus (HIV) or with chronic renal failure

Variables[a] (% of SVR)	Crude OR (p value)	Adjusted OR	95% CI	p value
Treatment				
Conventional IFN (27.1)	1.0	1.0	-	-
Pegylated IFN (35.3)	1.3 (0.353)	5.8	1.5-21.4	0.008
Interruption				
Yes (6.7)	1.0	1.0	-	-
No (39.0)	9.0 (0.000)	14.3	3.3-45.4	0.000
Cirrhosis				
Yes (15.2)	1.0	1.0	-	-
No (39.8)	3.7 (0.004)	7.7	2.5-33.3	0.002
Genotype				
1 (27.8)	1.0	1.0	-	-
Non-1 (37.5)	2.5 (0.295)	5.3	1.7-16.7	0.020

a: logistic regression model using stepwise backward technique Stata 8.2 (Stata Corporation, College Station, Texas, USA, 2005), with 142 of the 175 treatments. Fifty-five treatments were excluded from the model due to patient infected with HIV, chronic renal failure, treatment schedules without RBV or lack of information on the genotype, age or cirrhosis. Other non-associated variables included in the model were gender, age, nature of the health institution where the treatment took place (public or private), other comorbidities (diabetes mellitus, porphyria, hyperthyroidism, psoriasis, psychosis) and whether it was the initial treatment or a retreatment; CI: confidence interval; IFN: interferon; OR: odds ratio; p value of the model: 0.000; pseudo R^2: 0.17.

2006, Silva et al. 2007, Vigani et al. 2008, Almeida et al. 2009). Cirrhosis was one of the most important factors associated with treatment failure in our study, with only 15.2% of cirrhotic patients achieving an SVR (Table II).

The other variables associated with SVR, such as genotype 1, interruption of treatment and use of PEG-IFN, were also as expected. Another fundamental factor, which unfortunately could not be analysed in this study due to incomplete treatment information, was the RBV dosage. In the past few years, it has become increasingly clear that a larger dose of RBV is linked to therapeutic success (Davis et al. 1998, Zoulin et al. 1998, Mangia et al. 2010).

The SVR rates in therapy regimens that included PEG-IFN and RBV were similar among initial treatments (35.5%) and retreatments (34.8%). The good out-

TABLE IV

Comparison of sustained virologic response (SVR) rates in other studies[a] with those found in the present study

Site[b]	IFN type	Total (n)	SVR (%)	Gen 1 (%)	Non-1 gen (%)	Cirrhosis (%)	Type of study	Reference
Multicenter international	conv	505	47	67.9	32.1	27	Naïve[e],	Manns
	peg[c]	511	54	68.1	31.9		ITT,	et al. (2001)
	peg[d]	514	47	67.8	32.2		RCT	
Multicenter international	conv	444	44	62	38	12	Naïve,	Fied
	peg	453	56	65	35		ITT,	et al. (2002)
							RCT	
Rio de Janeiro	conv	202	30.2	71.6	28.4	15.3	Naïve,	Figueiredo-Mendes
							observational[f]	et al. (2003)
Rio Grande do Sul	conv	337	32	41.3	58.7	45.3	Naïve,	Alves
							ITT,	et al. (2003)
							observational	
São Paulo	conv	83	45.5	0	100	32.2	Naïve,	Vigani
	peg	97	36.2	100	0	15.3	observational	et al. (2008)
Multicenter Brazil	peg	134	33	72	28	34	Retreatment[e],	Parise
							ITT,	et al. (2006)
							RCT	
Rio Grande do Sul	peg	323	35.3	100	0	30.3	Naïve,	Almeida
							ITT,	et al. (2009)
							observational	
Multicenter Brazil	peg	67	54	60	40	10	Naïve,	Gonçales
							ITT	et al. (2006)
Multicenter Brazil	peg	26[g]	62	73	27	5	Retreatment,	Gonçales
	conv	40[h]	38	73	27	13	ITT	et al. (2006)
Paraná	conv	87	32.1	53.7	46.3	19.2	Naïve,	Acras
							observational	et al. (2004)
São Paulo	peg	58		100	0	26[i]	Naïve,	Silva
							ITT	et al. (2007)
Multicenter Brazil	peg	31	48	100	0	6.4	Naïve,	Brandão
		54	76	0	100	9.2	RCT	et al. (2006)
São Paulo	peg	130	26.8	70	30	10.8	Retreatment,	Gonçales
							ITT	et al. (2010)
Mato Grosso[j]	conv	56	28.6	22.9	77.1	21.8	Naïve,	Present
	peg	93	35.3	90.4	9.6	25	observational	study
Mato Grosso[j]	conv	3	0	33.3	66.7	66.7	Retreatment,	Present
	peg	23	34.8	54.5	45.5	43.5	observational	study

a: only studies which included treatment with RBV were considered. Studies performed on specific populations were excluded; *b*: named localities are Brazilian states; *c*: pegylated (peg) interferon (IFN) (1.5 mcg/Kg/week) for four weeks, afterwards 0.5 mcg/Kg/week; *d*: pegylated IFN (1.5 mcg/Kg/week) for the duration of the treatment; *e*: naïve patients; *f*: Phase 4 (observational); *g*: relapser patients; *h*: non-responder patients; *i*: 26% of patients with F3 or F4; *j*: excluded patients co-infected with human immunodeficiency virus or with chronic renal failure; conv: conventional; ITT: intention to treat; RCT: randomized controlled trial.

comes of retreatments compared with initial treatments was likely because 23 (88.4%) of the 26 retreatments were performed with PEG-IFN, most of them in patients who had received IFNc in their initial treatments.

However, when we analysed only the initial treatments of the non-1 genotype patients, 84% of whom were treated with IFNc, the SVR rate was 38.6%. A multicentre study of retreatment in Brazil, conducted by Parise et al. (2006), had demonstrated good results. The SVR rate reached in the initial treatment of non-1 genotype with PEG-IFN (71.4%) was higher than the SVR rate found in treatments with IFNc (32.4%), although the difference was not statistically significant. Some of the initial treatments were performed with PEG-IFN, contrary to Brazilian Federal Administrative Rule 34/2007, probably because the medication was provided under a judicial injunction or because these were cirrhotic patients. These data support the use of pegylated IFN for all genotypes from the start of the treatment, as is performed in other countries (Ghany et al. 2009, Brook et al. 2010), thus sparing patients from the greater risk of therapy failure and the need for a new course of treatments.

In short, this study analyses aspects of the treatment of chronic hepatitis C in MT in the first decade of the 21st century, showing SVR rates of approximately 30%. Numbers similar to these were found in studies carried out in other regions of the country in real-life situations. The sum of these results indicates the need to re-evaluate the protocol of the Brazilian Ministry of Health for the purpose of improving the effectiveness of the program to control hepatitis C in the country.

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