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EFFECTIVENESS OF ALPHA INTERFERON (+ RIBAVIRIN) IN THE TREATMENT OF CHRONIC VIRAL HEPATITIS C GENOTYPES 2 AND 3 IN A BRAZILIAN SAMPLE

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ABSTRACT – ***Context*** - Pharmacovigilance studies aim to detect, assess, understand and prevent risks of adverse effects of medications or any other possible drug related problem. Alpha interferon is being produced by Bio-Manguinhos/Fiocruz, Rio de Janeiro, RJ, Brazil and used in the treatment of chronic hepatitis C at Brazilian National Health System. ***Objective*** - To study the safety profile and effectiveness of alpha interferon in a sample of Brazilian patients with chronic hepatitis C genotypes 2 and 3, in Porto Alegre, RS, Brazil. ***Method*** - We followed a cohort of chronic hepatitis C genotypes 2 and 3 patients treated with alpha interferon plus ribavirin in a specialized outpatient clinic in southern Brazil. Adverse events were collected and classified according to severity in monthly structured interviews. To measure effectiveness, hepatitis C viral load was evaluated before, at the end and 24 weeks after the treatment. ***Results*** - We followed 141 patients during the study period, of which 52.5% were female with mean age of 52 years. The most frequent adverse events were fatigue (84%), headache (79%) and myalgia (75%). There were 13 treatment interruptions due to adverse events, 9 of those considered serious adverse events. Virological response at end of treatment was 54.6% and after 24 weeks 39.7%, considering all patients who started treatment. ***Conclusion*** - The product produced by Bio-Manguinhos has similar efficacy and adverse event and sustained virological response profiles comparable to those found in the literature. This is the first study of pharmacovigilance performed with the Brazilian product. These data will be useful for planning and management of this disease in Brazil.

HEADINGS – Hepatitis C, chronic. Interferon alpha. Ribavirin. Adverse drug reaction reporting systems.

INTRODUCTION

Chronic hepatitis C represents a major public health problem worldwide. The estimated average global prevalence is close to 3% (ranging from 0.1% to 5% in different countries). Therefore, there are about 175 million carriers of hepatitis C virus (HCV) worldwide[24]. Approximately 30% of infected patients develop cirrhosis in 20-30 years and 1%-4% are considered at high risk of developing hepatocellular carcinoma[23]. The chronicity of hepatitis C is characterized by persistent HCV for 6 months. Prospective studies show that 60% to 85% of these infections progress to chronicity[15, 24].

In Brazil, the treatment of chronic hepatitis C was established by Clinical Practice Guidelines for Chronic Viral Hepatitis C (CPG-HCV) of Ministry of Health (MoH) through Ministerial Decree, reviewed at 2011[6]. However, this study used the guideline of 2007, in force in the implementation period[5]. This guideline recommends that genotype 2 or 3 patients should be treated with alpha interferon (IFN) and ribavirin during 24 weeks; genotype 1 patients should be treated with peginterferon (PEGIFN) plus ribavirin for 48 weeks; it also recommends that treatment centers should be created to follow-up these patients[19].

The main adverse reactions described for IFN are headache, fatigue, depression, anxiety, irritability,

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insomnia, fever, dizziness, difficulty of concentrating, pain, alopecia, pruritus, dry skin, nausea, anorexia, diarrhea, abdominal pain, weight loss, muscle pain, viral infections, skin allergic reactions, hypothyroidism, vomiting, cough, sore throat and sinusitis[8, 20].

The verification of the adverse reactions of IFN was made only in phase III of randomized clinical trials in secondary analysis, in which the number of patients and clinical situations such as co-morbidities are limited. So it is very important that adverse reactions are evaluated after marketing in a large number of patients with other disorders.

Pragmatic trials of adverse drug reactions (ADRs) or pharmacovigilance aim to detect, assess, understand and prevent risks of adverse effects of medications or any other possible drug related problems in real life scenarios[4, 27].

Stricker and Psaty[25] - in a systematic review of studies for detection, quantification and verification of ADR - report the limitations of clinical studies to detect ADR of new drugs. They emphasize the importance of studies to detect ADR on post-marketing and the lack of a systematic process of verification and quantification of adverse reactions in the daily practice of health professionals.

Following the recommendation of MoH, the State Health Secretariat of Rio Grande do Sul (SES/RS) implemented in September, 2003, the first Center for Application and Monitoring of Injectable Drugs (CAMMI) at Sanatório Partenon Hospital (HSP) for care of patients with hepatitis C treated with PEGIFN associated to ribavirin. According to the same recommendation, in August, 2006, it expanded its service to patients treated with IFN, dispensing medicines and monitoring the treatment of this group of patients.

The aims of these services were to monitor the treatment through Pharmaceutical Care in order to promote better health care to patients with chronic hepatitis C; to reduce costs by optimizing the bottles of PEGIFN-2b; to create centers of active pharmacovigilance to users of these medicines within the health care system in Porto Alegre metropolitan area, able to generate scientific data of the new Brazilian product with IFN in clinical practice[3, 16].

Through these services a qualified health care environment was created which has allowed the full exercise of pharmaceutical care within the health care system with results measured both from the point of view of cost and effectiveness and patient adherence to treatment and in terms of satisfaction and gratification of users with respect to services[17].

The main objective of this study was to understand the safety profile and effectiveness of IFN produced by Bio-Manguinhos, combined with ribavirin, used in the treatment of chronic hepatitis C genotype non-1 in a sample of patients in the health care system in Porto Alegre, RS, Brazil.

METHODS

The study included patients who started treatment at (CAMMI-HSP), from August, 2007 to March, 2008.

Before the treatment the patients had an initial interview with a pharmacist, in which data related to the disease, co-morbidities, use of medications and laboratory tests were collected, and instructions on treatment were given.

The patients underwent subcutaneous treatment with 3,000,000 IU alpha interferon produced by Bio-Manguinhos/Fiocruz 3 times a week combined with ribavirin 1,000 to 1,250 mg/day orally for 24 weeks according to CPG[5]*. Longer treatments (48 weeks) were carried out in the case of extrahepatic manifestations and cirrhosis. Monotherapy was justified by chronic renal failure, which contraindicates the use of ribavirin.

Data collection

Data were collected by trained researchers, who used a specific collection card already used in the service routine. The Pharmacotherapeutics Card was used to record initial patient information and collection of adverse events and laboratory tests during treatment.

Before the beginning of the treatment patients underwent an initial structured interview with the pharmacist who collected data related to the disease, comorbidities, use of other drugs and laboratory tests; instructions on treatment were provided during this initial interview.

All patients were interviewed with an interval of 4 to 6 weeks. The interviews started with open questions about the general state of health and then with closed questions about events known to be frequent during treatment, using special anamnesis and recording the events reported in the database.

The information reported by patients was recorded in the adverse events collecting card. Laboratory tests were evaluated after each interview, according to the schedule established.

The following circumstances were considered as lethal or serious adverse events (SAE), death during the study period, life-threatening events, events that required hospitalization, clinical or laboratory events leading to the suspension of the drug or incapacitating events[9, 26].

The patients were asked to complete a diary during the treatment, recording the places of the applications and application-related events.

Immediately after completion of treatment and 24 weeks thereafter, patients were instructed to perform examinations of qualitative PCR of HCV virus. Patients who did not return for assessment were contacted by telephone or letter.

Statistical analysis

A database was developed in Access and analyzed using Statistical Package for the Social Sciences (SPSS) 14.0. The WHO Adverse Reactions Terminology (WHO-ART) was used. The descriptive analyses were performed using mean ± standard deviation for continuous variables and also absolute and relative frequencies for categorical variables.

Ethical aspects

This study was evaluated by Ethics in Research Com-

* Author's note: this study was conducted in the period preceding the publication of the new guideline in May, 2011.

mittee of School of Public Health, Porto Alegre, RS, and approved under number 311/07. Before the treatment all patients signed a Free Informed Term of Consent with confidentiality assured.

RESULTS

We allocated 141 patients from August 2007 to March 2008. The characterization of the sample at baseline is shown in Table 1. Of the 141 patients, 86 had some co-morbidity (61%), the most frequent being hypertension (42/141- 29.8%), depressive symptoms (13/141 - 9.2%) and diabetes (11/141 - 7.8%). Ninety-two patients used some kind of medication prior to initiation of therapy with IFN and ribavirin (64.5%). The most common were hydrochlorothiazide (11/141), propranolol (10/141), omeprazole (5/141) and paracetamol (5/141).

TABLE 1. Sample characterization

	Sample	
Number of patients	141	
Gender n (%)		
Male	67 (47.5)	
Female	74 (52.5)	P = 0.554
Mean age ± dp	51.8 ± 9.8 years	
HCV genotype: n (%)		
2	22 (15.6)	
3	119 (84.4)	
Comorbidities: n (%)	86 (61)	
Hypertension	42 (29.8)	
Emotional disturbances	13 (9.2)	
Diabetes	11 (7.8)	
Use of medicines on the beginning of the treatment: n (%)	92 (64.5)	

TABLE 2. Degree of necroinflammatory activity and fibrosis

Activity/Fibrosis	No. of patients	%
A0/F2	1	0.7
A1/F0	2	1.4
A1/F1	8	5.7
A1/F2	17	12.1
A1/F3	3	2.1
A1/F4	7	5.0
Subtotal	**38**	**26.9**
A2/F1	7	5.0
A2/F2	30	21.3
A2/F3	22	15.6
A2/F4	7	5.0
Subtotal	**66**	**46.8**
A3/F2	1	0.7
A3/F3	6	4.3
A3/F4	8	5.7
Subtotal	**15**	**10.6**
F4	5	3.5
Subtotal	**124**	**87.9**
Not classified	**17**	**12**
Total	**141**	**100**

Evaluation of liver damage was demonstrated before the start of treatment by liver biopsy by Metavir classification. As regards the degree of necroinflammatory activity and fibrosis, 123 patients had results of activity and fibrosis. Of these, 118 underwent liver biopsy and 5 presented a medical report or endoscopy showing esophageal varices being classified as F4 (Table 2). The reasons for not performing liver biopsy were contraindication due to hemophilia and thrombocytopenia or in cases with advanced clinical signs of disease (presence of esophageal varices). The percentage of cirrhotic patients in the study population was 19.2%, among all types of necroinflammatory activity presented.

Of the 141 patients, 128 underwent treatment for 24 weeks with alpha interferon associated with ribavirin; 12 patients for 48 weeks with alpha interferon associated with ribavirin; and 1 patient for 48 weeks with alpha interferon monotherapy. Longer treatments were carried out in the case of extrahepatic manifestations and cirrhosis. Monotherapy was justified by chronic renal failure, which contraindicates the use of ribavirin.

Adverse events

The patients reported 115 adverse events and 4437 occurrences. Figure 1 shows the absolute number of adverse events per month after starting treatment, and Figure 2 shows the five most frequently reported ones.

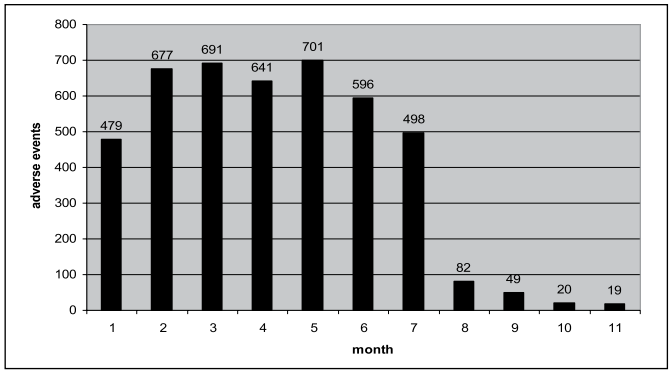

FIGURE 1. Absolute number of adverse events per month of treatment

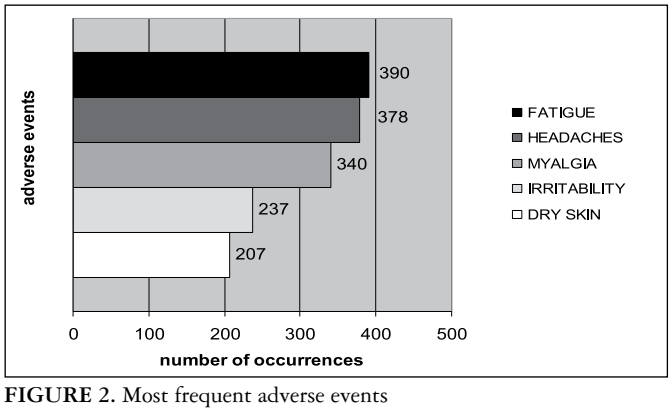

FIGURE 2. Most frequent adverse events

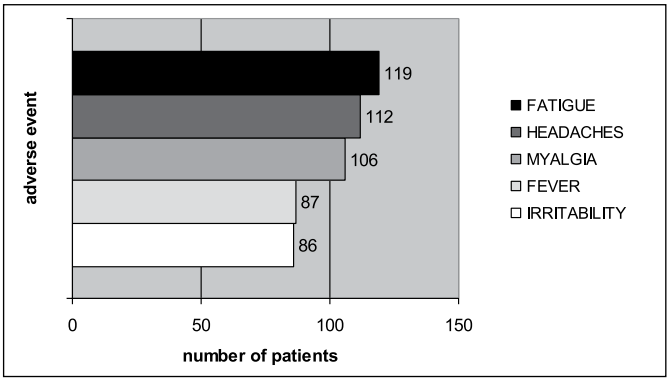

FIGURE 3. Prevalence of adverse events per patient

The frequency of adverse events per patient was also analyzed, as shown in Figure 3. In this analysis the whole event, even if reported more than once during treatment, was considered as one occurrence. The most frequent events were fatigue (84%), headache (79%), myalgia (75%), fever (62%) and irritability (61%). The number of events per patients of cirrhotic patients was 23.9 ± 16.4 and non cirrhotic patients was 28.4 ± 18.1 (P = 0.25).

There were 14 treatment interruptions (14/141 - 10%), 13 of which due to adverse events and one due to waiver by the patient. Of these events, 9 were classified as SAE, namely: rupture of esophageal varices, syncope (2 cases), pneumonia, hyponatremia, migraine and cystitis (events that required hospitalization). No patient died during the study period.

Adverse events at the place of application

The patients recorded 7658 applications on the diary, including place of administration on 1707 of these records. Among these the most frequent local event was erythema, representing 62.6%, followed by pain (20.5%) and burning (10%).

Laboratory changes

The blood dyscrasias observed during treatment with IFN combined with ribavirin were anemia (39.6%), leukopenia (4.4%), neutropenia (3.7%) and thrombocytopenia (3.7%). Table 3 shows the percentages of patients with such changes at some time during treatment, according to cutoff points established that determine clinical relevance.

TABLE 3. Number/percentage of patients with laboratory abnormalities below the established cutoff point

	n (%)
Anemia (> 10.0 g/dL)	40 (39.6)
Neutropenia (> 750/mm³)	5 (3.7)
Leukopenia (> 1500/mm³)	6 (4.4)
Thrombocytopenia (> 50.000/mm³)	5 (3.7)

Monitoring of patients' weight

The patients were weighed once a month, presenting an average weight of 71.25 kg (± 20.7) at baseline and 71.10 kg (± 15.5) at the end of 6 months of treatment (P = 0.953).

Adjuvant treatments for relief of symptoms associated with adverse event

During the entire monitoring period, 330 (7.4%) adverse events were associated with the use of adjuvant treatments, a total of 4437 occurrences of adverse events reported.

Twenty-three patients received some type of medication during treatment. Among the percentage (7.4%) of adverse events that were associated with the use of adjuvant therapies the most commonly used drugs were acetaminophen (79%) and dipyrone (3%).

Seven patients used epoetin alpha as erythrocyte-stimulating factor to control anemia due to the use of ribavirin.

Three patients received filgrastim as a granulocyte stimulating factor for control of neutropenia and leukopenia.

Virological response

The analysis of virological response (VR) and sustained virological response (SVR) were made using the qualitative PCR presented by all patients after completion of treatment and 24 weeks after that for patients with negative results in the first analysis. The search was conducted through interviews arranged in the care center or telephone contact with patients.

All patients who received at least one dose of medication were considered in the analysis. Of the 141 patients enrolled, 77 patients had negative PCR results at the end of treatment (VR = 54.6%) and 56 patients remained negative 24 weeks after completion of treatment (SVR = 39.7%). This analysis considered the patients that did not receive PCR with positive result (Table 4). Figure 4 illustrates an overview of the analysis of virological response in the study.

TABLE 4. Virological response (VR) and sustained virological response (SVR)

	n	%VR	n	%SVR
Positive PCR	44	35.4	61	50.3
Negative PCR	77	54.6	56	39.7
Follow-up losses	6*		10*	
Total	141	141 (100%)	141 (100%)	141 (100%)

*considered with positive PCR result

DISCUSSION

We performed the first active pharmacovigilance of IFN produced by Bio-Manguinhos/Fiocruz combined with ribavirin in a health care environment which represents a breakthrough as regards the promotion of activities which promote the rational use of medicines.

We identified that in practice patients have comorbidities, which in a perfect setting for a randomized clinical trial would not be possible to cover. Randomized controlled trials (RCT) use as exclusion criteria precisely the most frequent comorbidities in the general population, which are cardiovascular diseases, decompensated diabetes, psychiatric illness, HIV+, anemia, epilepsy, hemophilia and autoimmune diseases[13, 14, 18]. This may have caused a higher incidence of

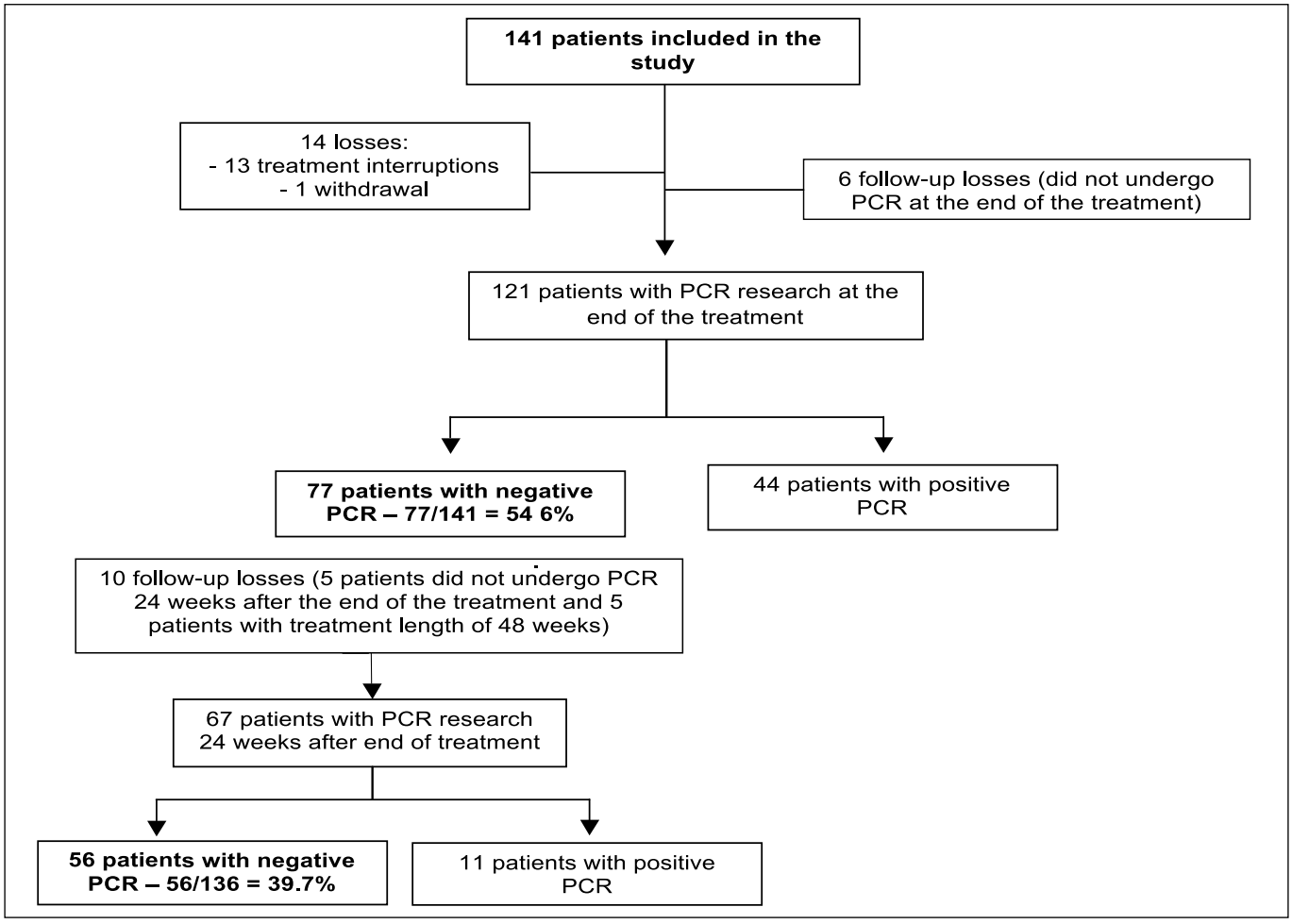

FIGURE 4. General design of VR and SVR analisys

adverse events and complications of pre-existing illness, given that the literature reveals that prior co-morbidities should be strictly monitored during treatment, with a relative contraindication for such morbidities[8].

With regard to the percentage of patients with advanced disease, we noted that 19.4% already had established cirrhosis. Compared with RCT, the presence of cirrhosis in patients ranges from 4% to 7%[13, 14].

Patients with cirrhosis are considered at higher risk and may prematurely discontinue treatment for encephalopathy, ascites or rupture of esophageal varices. In the present study only one patient had interruption due to adverse events associated with decompensated cirrhosis (rupture of esophageal varices). Studies in literature also excluded patients with decompensated cirrhosis, which in practice may also reflect a worsening in the manifestations as to the severity and frequency of adverse events.

The profile of reported adverse events was similar to those observed in other clinical trials. However, the prevalence of all adverse events in this study was higher compared to studies found in medical literature[21]. Fatigue and headache were the most frequently reported events in this study as well as in literature, though with higher prevalence. While clinical studies show the percentage of fatigue ranging from 50% and 68%, and headache from 52% to 63%, in this study we found percentages of 84.4% and 79.4%, respectively[11, 13, 14, 18]. Among the 10 most frequently reported events, the following are highlighted: myalgia, fever, irritability, anorexia, dry skin, arthralgia, alopecia and leg pain. Also in relation to occurrence of adverse events, we found that 9% of the patients discontinued treatment prematurely due to an adverse event. Only one patient abandoned the treatment with no explanation. In an analysis of patients from Rio Grande do Sul in 1999 and 2000 treated with alpha interferon and ribavirin, 11,7% of the sample stopped treatment early (95% due to adverse events and 5% due to dropout)[2].

During the study nine serious adverse events occurred, three of which led to discontinuation of treatment (hyponatremia, rupture of esophageal varices and exacerbation of migraine). No deaths occurred during the study. Although unusual, hyponatremia has been reported in the literature in a patient using alpha interferon for the treatment of chronic myeloid leukemia[12], secondary to syndrome of inappropriate secretion of antidiuretic hormone.

The incidence of events at the place of application was 22.3%. Among the recorded events, the most reported was erythema (62%), followed by pain (20%) and burning sensation (10%). Clinical studies show incidence rates of 12% to 36% of events at the place of application[13, 14].

In summary, treatment with IFN produced by Bio-Manguinhos, combined with ribavirin for 6 to 12 months of treatment showed an adverse event profile similar to that reported in the literature. Although a higher frequency of serious events was found, we believe that the difference is due to the high prevalence of co-morbidities in this population, and especially, to the active and monthly search for adverse events, a methodology that increases the reports of complaints compared with other studies that focus or are based on spontaneous reports[10]. Furthermore, we showed that the profile of adverse events did not differ from that expected for the pharmacodynamic profile of alpha interferon and ribavirin, and all events had a resolution with specific treatment.

Regarding VR, considering the number of patients who started treatment and received at least one dose of the drug, the percentage was 54.6%, since in this case we considered the 141 patients who were followed in study time, including those who have not reached the end of therapy (interruptions due to adverse events or withdrawal by the patient). Compared to an effectiveness study conducted in Rio Grande do Sul in 1999 and 2000, which included in its sample genotype 1 patients, the VR at the end of the treatment was 49%[2]. In another effectiveness study held in the State of Paraná/Brazil from 1999 to 2002, a VR rate of 42.5% was obtained[1].

Clinical trials carried out by Poynard et al.[18] and McHutchison et al.[14] evaluated the VR and SVR after treatment with IFN with or without ribavirin for 24 or 48 weeks of treatment. Patients of all genotypes were included in the sampling and VR analyses were not stratified by genotype. Thus, the VR at the end of the 24 weeks treatment with IFN and ribavirin in these studies were 57% and 53%, respectively. Importantly, in the first study the sample of patients with genotype 1 represented 58% and 72% of the sample, respectively.

In our sample SVR was 39.7%, because we considered even those who have not reached the end of therapy (interruptions due to adverse events or withdrawal) or have not achieved VR at the end of treatment.

In studies conducted in the States of Rio Grande do Sul and Paraná/Brazil, SVR rates were 39% and 45%, respectively, in patients with genotype non-1[1, 2]. And in the studies by Poynard et al.[18] and McHutchison et al.[14] the rates were 64% and 69%, respectively, with stratification by genotype.

Systematic reviews report that some features are related to a better response to antiviral treatment; among them are low or moderate viral load, mild or absent degree of fibrosis, genotypes 2 and 3, age of 40 years or less, and weigh of less than 75 kg[22, 28]. Among patients of genotypes 2 and 3, low viral load and absence of advanced fibrosis and cirrhosis are considered predictive factors of better response to treatment for 24 weeks[7].

In a recent update of the Brazilian Guideline for the treatment of chronic hepatitis C, patients of genotypes 2 and 3 which do not present these predictive factors of response to treatment should be treated with alpha peginterferon and ribavirin for 24 to 48 weeks[6], option not contemplated in the previous guideline of 2007[5], in force at the time of completion of this study.

In this study, VR e SVR rates were similar to those found in local studies of effectiveness, and below the main clinical trials found in literature. In this respect, it is important to emphasize that this is a follow-up study of patients treated in a real life scenario of Brazilian public health system, reflecting the reality of our health care system, different from the reality of a clinical trial where the inclusion criteria are extremely strict and approach to patient is done differently.

CONCLUSION

The combination of IFN and ribavirin in the study sample showed a profile of adverse events as expected and SVR similar to local studies of effectiveness for this treatment, ensuring the safety and effectiveness of the medicine produced by Bio-Manguinhos. SVR are expected to be lower than RCT due to different population's characterists and co-morbidities.

Gonçalves CBT, Amaral KM, Sander GB, Martins NLC, Pereira L, Picon PD. Efetividade da alfainterferona (+ribavirina) no tratamento da hepatite viral crônica C genótipos 2 e 3 em amostra brasileira. Arq Gastroenterol. 2012;49(2):150-6.

RESUMO – ***Contexto*** - Estudos de farmacovigilância têm por objeto a detecção, avaliação, compreensão e prevenção dos riscos dos efeitos adversos dos medicamentos ou qualquer outro possível problema relacionado com medicamento. A alfainterferona (IFN) está sendo produzida por Bio-Manguinhos/Fiocruz e utilizada no tratamento da hepatite C crônica no âmbito do Sistema Único de Saúde (SUS). ***Objetivo*** - Conhecer o perfil de segurança e efetividade deste IFN em uma amostra de pacientes brasileiros com hepatite crônica pelo vírus C genótipos 2 e 3, em Porto Alegre, RS, Brasil. ***Método*** - Trata-se de uma coorte de pacientes com hepatite crônica pelo vírus C genótipos 2 e 3 tratados com IFN e ribavirina e acompanhados em um serviço ambulatorial especializado no sul do Brasil. Os eventos adversos foram coletados e classificados de acordo com a gravidade em entrevistas mensais estruturadas. Para medida de eficácia foi avaliada a carga viral do HCV antes, ao final e 24 semanas após o término do tratamento. ***Resultados*** - Foram acompanhados 141 pacientes no período do estudo, sendo 52,5% do sexo feminino com média de idade de 52 anos. Os eventos adversos mais frequentes foram fadiga (84%), cefaleia (79%) e mialgia (75%). Ocorreram 13 interrupções de tratamento por eventos adversos, sendo nove destes considerados eventos adversos graves. A resposta virológica ao final do tratamento foi de 54,6% e 24 semanas após de 39,7%, considerando todos os pacientes que iniciaram o tratamento. ***Conclusão*** - O produto produzido por Bio-Manguinhos possui eficácia e um perfil de eventos adversos e de resposta virológica sustentada comparáveis aos encontrados na literatura. Este é o primeiro estudo de farmacovigilância realizado com o produto brasileiro. Estes dados serão úteis para planejamento e gestão do tratamento desta doença no Brasil.

DESCRITORES – Hepatite C crônica. Interferon alfa. Ribavirina. Sistemas de notificação de reações adversas a medicamentos.

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