Side effects of the hepatitis C treatment at the ABC application center

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Summary

Objective: To review and compare side effects of hepatitis C treatment with pegylated interferon and ribavirin at the CRIE of the Hospital Mário Covas (Santo André), São Paulo, Brazil, from February 23 to May 5, 2011. **Methods:** Cross-sectional study through questionnaire, with a non-probability sample comprised of 340 patients that had received at least one dose of the medication. **Results:** Side effects presented were fatigue (82.9%), arthralgia and/or myalgia (76.8%), weight loss (71.8%), headache (67.6%), listlessness (65.9%), depression and/or irritability (64.4%), itching (60.6%), fever (59.1%), alopecia (51.5%), dry cough (34.1%), nausea (11.7%), inappetence (11.7%), and dizziness (7.9%). Up to 19 symptoms were reported during treatment. Only four patients (1.2%) did not present side effects. When comparing the types of interferon, it was observed that alpha-2b caused an average of 8.01 symptoms per patient, while alpha-2a was responsible for an average of 7.50 symptoms. Patients using interferon alpha-2b showed more fever, weight loss, headache, arthralgia and/or myalgia, fatigue, listlessness, depression and/or irritability, and dry cough than patients using alpha-2a, who had more alopecia and itching. **Conclusion:** The study shows a high morbidity related to the treatment, as only 1.2% of the patients showed no side effects. In the sample, the pegylated interferon alpha-2b was responsible for higher prevalence of fever and weight loss when compared to alpha-2a, and this was a statistically significant relation ($p < 0.05$).

Keywords: Hepatitis C; combined therapy; interferon alpha-2a; interferon alpha-2b; ribavirin.

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Introduction

It is estimated that the hepatitis C virus (HCV) infects 3% of the world's population, which corresponds to 210 million people, and of these, 80% develop to the chronic stage of the disease[1,2]. According to the World Health Organization (WHO), Brazil is considered a country with intermediate endemicity for hepatitis C, with a prevalence between 2.5% and 10%[3].

The process of selection and adaptation to the host caused the virus to evolve into different HCV genotypes. The most used classification, proposed by Simmonds, et al., defines six different types, with subtypes 1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4a, 5a, and 6a. Although the criterion is based on molecular biology, this classification has practical, pathogenic, epidemiologic, and treatment-related implications. For example, subtype 1b may cause severe forms of the infection and it, along with type 4, respond less favorably to treatment with interferon (IFN). Therefore, these genotypes should be treated for a longer period (48 weeks). In Brazil, about 2/3 of the patients have genotype 1, followed by type 3, with approximately 20% to 30%, and type 2 in a lower proportion[4].

The virus is transmitted mainly through contact with infected blood by percutaneous exposure: sharing of equipment for intravenous drug use (18%) or personal-care items, such as razors, toothbrushes, and manicure/pedicure equipment. Additionally, it can be transmitted via tattooing and piercing, transfusion of blood and/or blood products (16%), organ transplantation from infected donors, and vertical and sexual transmission (9%)[1,2,5,6]. In the cases reported in the Viral Hepatitis Epidemiological Bulletin, a high percentage of unknown transmission route is observed (43%)[6].

It is estimated that 15% to 45% of the individuals who had contact with HCV present spontaneous elimination of the virus, 25% of them have a mild disease[7], while 55% to 85% develop to the chronic progressive form of the disease. Spontaneous clearance of the virus is more frequent in symptomatic cases of acute hepatitis C and in patients affected by genotype 3. This usually occurs on the first 12 weeks after the beginning of the disease[8]. Most patients that develop to the chronic form also develop fibrosis. Death may occur as a result of complications, as cirrhosis and hepatocellular carcinoma[7,9,10]. It is estimated that 20% to 25% of the patients with fibrosis develop to cirrhosis in a period that may vary from 10 to 30 years[7]. Hepatocellular carcinoma often occurs in patients with cirrhosis, with an incidence of around 1% to 4% per year[9].

The objective of the treatment of chronic hepatitis C is to control the liver disease progression through inhibition of viral replication[11]. Therefore, the treatment targets are sustained virological response (SVR), increase in life expectancy and improvement of quality of life, decrease of the probability of development to terminal hepatic insufficiency (reduced inflammatory activity prevents the progression to cirrhosis and hepatocellular carcinoma), and reduction in the risk of transmitting the disease[2].

In order to determine the treatment, the risk of disease progression, likelihood of therapeutic response, adverse effects of the treatment, and presence of comorbidities must be considered[2].

Treatment of chronic forms is based on the combination of IFN or pegylated interferon (PEG-IFN) with ribavirin (RBV) for a period of 48 to 72 weeks, depending on the genotype found, with clearance of approximately 80% for viral genotypes 2 and 3, and of around 40% for genotype 1[1,2,12-17].

In general, sustained virological response rates in genotypes 2 and 3 are higher than those found in genotype 1, regardless of the treatment strategy adopted[18,19].

In Brazil, conventional IFN and RBV are available, both produced in Brazil, as well as PEG-IFN alpha-2a and alpha-2b, produced by different pharmaceutical companies[12].

Current evidence is insufficient to indicate a preferred PEG-IFN formulation, due to similar efficacy and safety when the outcomes of SVR and toxicity are taken into account[2].

Hepatitis C treatment with IFN and RBV produces several laboratory abnormalities and potential side effects that require more stringent clinical and laboratory monitoring, aiming at improving the adherence to treatment and dose adjustment[20].

Acknowledged side effects of the therapy with conventional IFN and PEG-IFN are: alopecia, anemia, autoimmune disorders, depression or mood disorders, diarrhea, symptoms similar to influenza, pain or erythema at the injection site, retinopathy, sleep disorders, thrombocytopenia and neutropenia, thyroid dysfunction, and weight loss[2].

With respect to RBV, acknowledged adverse effects are: hemolytic anemia, cough, dyspnea, gout, nausea, rashes, and teratogenicity[2].

Deterioration in quality of life during treatment may have a negative impact on the patient's trust and may contribute to an unfavorable clinical outcome. Multidisciplinary support in approaching side effects, with support and motivation strategies, helps to reduce the risk of early treatment interruption[2].

In Hospital Estadual Mario Covas (HEMC) there are on average 300 to 350 patients that come once a month to the Reference Center for Special Immunobiologicals (CRIE) for treatment of hepatitis C. Due to the long-term treatment (usually six to 12 months), it is possible to find patients starting and finishing treatment all year round. Treatment interruption rate is around 2% to 5% per month, whether by medical guidance to suspend treatment due to side effects, or without justification.

In January 2012, the hepatitis C treatment interruption rate in the CRIE of the HEMC was of 2%. 100% of the patients that interrupted treatment were using interferon alpha-2b associated with RBV, of which 75% were using due to medical indication. Conversely, in February 2012, the interruption rate was 5.2%. Of the patients using interferon alpha-2b associated with RBV, 2.4% interrupted the treatment, of which 60% did so by medical guidance, while the interruption of treatment with interferon alpha-2a associated with RBV was 2.8%, of which 50% was due to medical indication.

Objective

To analyze and compare major side effects of hepatitis C treatment with PEG-INF (alpha-2a or alpha-2b) and RBV in the application center of the CRIE of the HEMC, Santo André, São Paulo (SP). To inform healthcare professionals working at HEMC of the effects of the treatment and possible improvements in patient support strategies.

Methods

The study, approved by the Ethics Committee of the FMABC (ABC Medical School), protocol CEP/FMABC No. 004/2011, had a descriptive nature and was carried out through a questionnaire applied by academics. The study population was comprised of patients being treated for hepatitis C with PEG-IFN (alpha-2a or alpha-2b) and RBV, during the period from February 23 to May 5, 2011, after agreeing to participate and signing the informed consent.

A non-probability sample was adopted for convenience, in which were interviewed 340 patients with hepatitis C being treated with PEG-IFN (subcutaneously) and RBV (oral) who had received at least one dose of the medication. None of the patients refused to answer the questionnaire and there were no absences. Patients that would have started treatment during the study period and who had not yet received any dose of the medication were excluded, some of whom were subsequently included in the study after receiving the first dose of the treatment.

Treatment was chosen by each patient's physician regarding dosage, duration of treatment, and type of PEG-IFN, but, in general, they followed the guidelines imposed by the Brazilian Ministry of Health, the State of São Paulo Health Department, and by various consensuses among medical specialties.

A single instrument applied to each subject was used, which was the questionnaire: "Hepatitis C Statistics – Patients in Treatment," prepared by the team itself. It had a set of 15 closed questions, multiple choice or fill in the blank, covering different aspects of the patient's life, such as: identification (date of birth, gender, race); health plan, if any; education; socioeconomic status; city of residence; diagnosis; virus genotype; medication used (PEG IFN alpha-2a or alpha-2b associated with RBV); possible transmission route; side effects of treatment; related diseases; and whether it was the first treatment or a recurrent disease treatment.

A descriptive analysis of all study variables was performed. Qualitative variables were presented as absolute and relative values. Quantitative variables were presented their central tendency and dispersion values. The chi-squared test, which compares percentage values (proportions), was used in order to verify the association between qualitative variables. For quantitative variables, homogeneity in the variances and adherence to the normal curve were verified by Levene and Kolmogorov-Smirnov tests, respectively. The significance level was set at 5%. The statistical software used was the Statistical Package for the Social Sciences (SPSS) 16.0 for Windows.

Among the methodological limitations of the study, 4% of the questionnaires were erroneously completed. The missing data were limited to socioeconomic status, gender, ethnicity, and health plan, if any; there was not, therefore, any errors in providing information regarding side effects. The presence of side effects was based on data informed by patients, with no objective measurement of the variables of interest.

Another limitation was the fact that neither the duration of treatment nor the clinical stage of hepatitis C was considered.

Results

340 individuals were interviewed, with ages varying from 23 to 83 years old, averaging 48.91 years; regarding gender, 172 (55.5%) were men and 138 (44.5%) women, racially distributed among white (233 – 69.1%), black (19 – 5.6%), mixed-race (80 – 23.7%), and Asian (5 – 1.5%).

Regarding the place of residence, 114 (33.5%) resided in Santo André, 123 (36.2%) in São Bernardo do Campo, 19 (5.6%) in São Caetano do Sul, 40 (11.8%) in Diadema, and 44 (12.9%) in other municipalities (São Paulo, Mauá, Ribeirão Pires, Grajaú, and Rio Grande da Serra).

Regarding education, eight (2.4%) subjects were illiterate, 109 (32.1%) completed primary school, 137 (40.3%) completed high school, 30 (8.8%) did not complete post-secondary education, and 56 (16.5%) completed post-secondary education.

With respect to socioeconomic status, 67 (20.5%) had an income below the minimum wage, 219 (67%) between two and six minimum wages, and 41 (12.5%) six or more minimum wages. In the sample, 155 (45.9%) had a healthcare plan, and 183 (54.1%) did not.

Of the possible routes of transmission indicated in the questionnaire, the following was observed: 22 (6.5%) via

tattooing or piercing, 17 (5.0%) via intravenous drugs, 96 (28.2%) via blood transfusion, 9 (2.6%) via sexual intercourse, 46 (13.5%) by another route, three (0.9%) via two of the abovementioned ways, and 147 (43.2%) did not know or did not want to inform. Manicure/pedicure, surgery, dental treatment, vertical transmission, accident with sharp objects, alcoholism, and bronchitis treatment were also mentioned.

Genotypes reported were: 126 (69.2%) genotype 1, 31 (17%) genotype 2, 22 (12.1%) genotype 3, and three (1.6%) genotype 4. A large part of the sample (158 patients – 46.5%) did not know the viral genotype.

Of the patients, 106 (28%) had related diseases, while 234 (68.8%) did not. The main comorbidities reported were systemic arterial hypertension (47 patients – 28%), diabetes mellitus (28 – 17%), and human immunodeficiency virus (HIV) positive (9 – 5%).

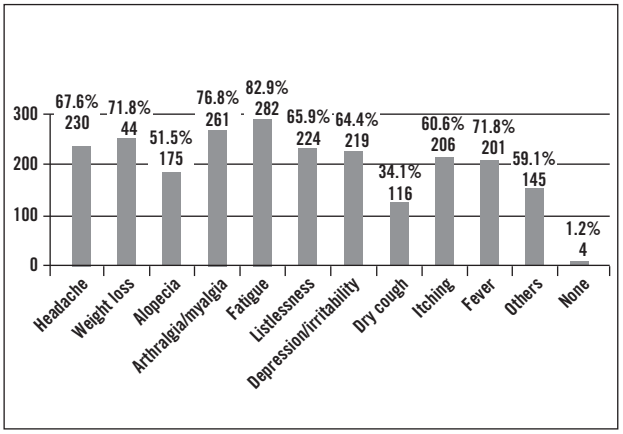
As to the medication (PEG-IFN) used, 181 (55.5%) patients used alpha-2b and 145 (44.5%) used alpha-2a, both associated with RBV. Most of patients (274 – 81.1%) were in their first treatment.

Over half of the patients reported fatigue, arthralgia and/or myalgia, weight loss, listlessness, depression and/or irritability, itching, fever, and alopecia during treatment (Graph 1).

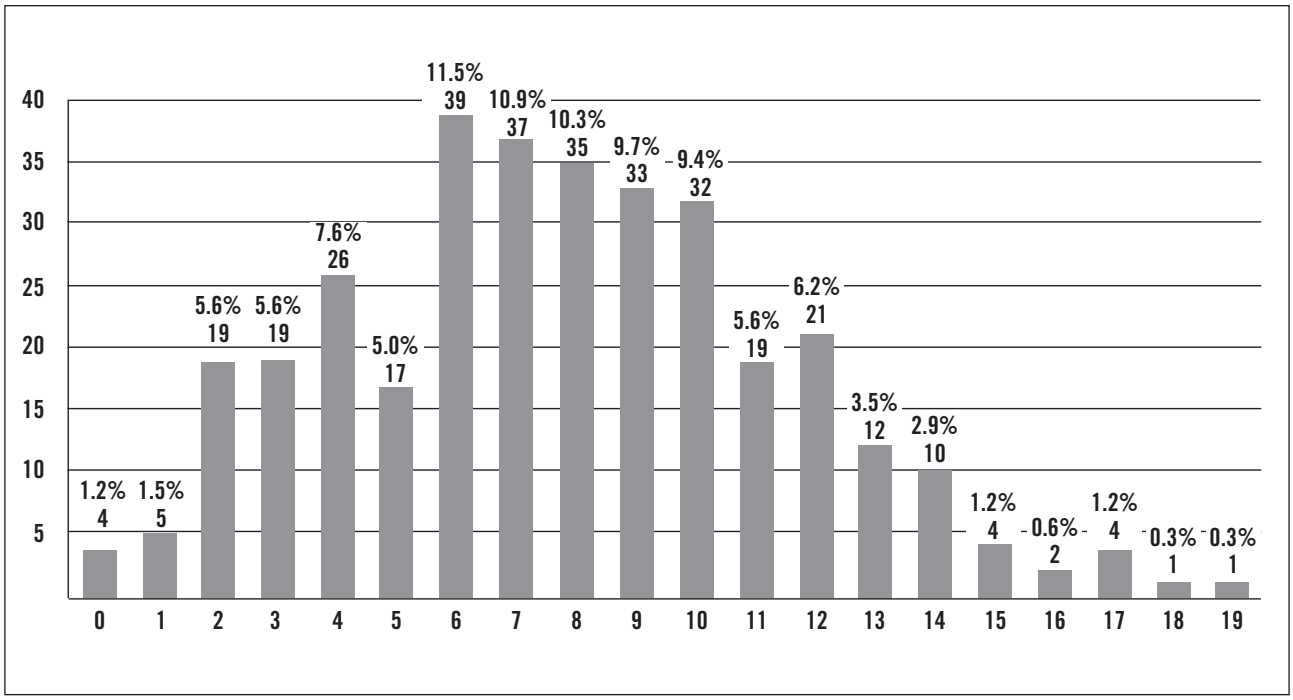
It was also observed that 145 (42.6%) patients presented other side effects that were not listed in the questionnaire, including nauseas (40 – 11.7%), inappetence (40 – 11.7%), dizziness (27 – 7.9%), anemia (21 – 6.1%), vomiting (16 – 4.7%), change in taste (14 – 4.1%), epigastralgia (11 – 3.2%), insomnia (11 – 3.2%), xerostomia (10 – 2.9%), chills (8 – 2.3%), malaise (7 – 2.0%), diarrhea (7 – 2.0%), erythema (6 – 1.7%), epistaxis (6 – 1.7%), somnolence (5 – 1.4%), cramps (4 – 1.1%), memory loss (4 – 1.1%), canker sores (4 – 1.1%), among others.

Interviewed patients reported zero to 19 symptoms. Only 4 (1.2%) patients in treatment did not present any type of side effect to the medication (Graph 2).

Comparing the number of side effects caused by PEG-IFNs, it was verified that of the 181 patients using alpha-2b and RBV, there was an average of 8.01 symptoms per patient (DP: 3.696); this average was 7.50 symptoms per patient (DP: 3.718) among the 145 patients using alpha-2a and RBV.



Graph 2 – Main side effects of hepatitis C treatment with pegylated interferon combined with ribavirin.



Graph 1 – Number of total side effects presented by patients at some point of the hepatitis C treatment with pegylated interferon combined with ribavirin.

Patients using interferon alpha-2b and RBV presented more fever, weight loss, headache, arthralgia and/or myalgia, fatigue, listlessness, depression and/or irritability, and dry cough than patients using interferon alpha-2a and RBV, who had more alopecia and itching. There was a statistical significance only in results regarding fever and weight loss (both with p = 0.001 [p=0,000]) (Table 1).

Discussion

The main transmission route reported was by blood transfusion; a great number the patients did not want to report or did not know the route of transmission. According to the Viral Hepatitis Epidemiological Bulletin, the highest proportions of cases are related to drug abuse and transfusion of blood and/or blood products, and a high percentage of unknown cause is equally found[6].

Table 1 – Association between side effects of hepatitis C treatment with the use of both types of pegylated interferon (both combined with ribavirin)

Treatment	Side effects (%)	Chi-squared test
Fever		
Peginterferon alpha-2a	66 (45.5%)	p = 0.001
Peginterferon alpha-2b	126 (69.6%)	
Weight loss		
Peginterferon alpha-2a	90 (62.1%)	p = 0.001
Peginterferon alpha-2b	145 (80.1%)	
Headache		
Peginterferon alpha-2a	91 (62.8%)	p = 0.064
Peginterferon alpha-2b	131 (72.4%)	
Alopecia		
Peginterferon alpha-2a	76 (52.4%)	p = 0.701
Peginterferon alpha-2b	91 (50.3%)	
Arthralgia and/or myalgia		
Peginterferon alpha-2a	108 (74.5%)	p = 0.547
Peginterferon alpha-2b	140 (77.3%)	
Fatigue		
Peginterferon alpha-2a	118 (81.4%)	p = 0.629
Peginterferon alpha-2b	151 (83.4%)	
Listlessness		
Peginterferon alpha-2a	95 (65.5%)	p = 0.800
Peginterferon alpha-2b	121 (66.9%)	
Depression and/or irritability		
Peginterferon alpha-2a	94 (64.8%)	p = 0.945
Peginterferon alpha-2b	118 (65.2%)	
Dry cough		
Peginterferon alpha-2a	48 (33.1%)	p = 0.747
Peginterferon alpha-2b	63 (34.8%)	
Itching		
Peginterferon alpha-2a	89 (61.4%)	p = 0.678
Peginterferon alpha-2b	107 (59.1%)	
Others		
Peginterferon alpha-2a	67 (46.2%)	p = 0.446
Peginterferon alpha-2b	76 (42.0%)	

The level of significance considered was 5% ($p < 0.05$)

It can be observed that there is prejudice and lack of information regarding the transmission of hepatitis C; for this reason, there were reports of anecdotal transmission routes in the questionnaires, such as alcoholism and bronchitis treatment. Additionally, the acquisition of false data is possible, since many patients may feel embarrassed and uncomfortable to answer how they became infected.

A large part of the patients did not know their disease genotype, while of those who knew, genotype 1 was the most prevalent, consistent with the study by Campiotto et al, who found that this type is the most prevalent in São Paulo. The second most reported genotype was genotype 2, followed by genotypes 3 and 4, diverging from Campiotto's study, which found the percentages in the following sequence: 1, 3, 2, 4, and 5[21].

A methodological limitation of the study was that patients were not questioned about how long they had been in treatment, as it is expected that patients with longer-term treatments have more side effects, nor were they questioned about the clinical stage of the disease. These data could be potential confounding factors in the study.

There were no objective measurements of the variables of interest, and side effects were based only on information provided by patients.

Another limitation was the fact that 4% of patients did not provide some data in the questionnaire (socioeconomic status, gender, ethnicity, and healthcare plan). The lack of this information did not impair the statistical analysis of the side effects, as missing data were limited to sample characterization.

The study shows high morbidity related to the treatment, as only 1.2% of the patients showed no side effects. This data is corroborated by McGowan et al., who reported that virtually all patients experience some side effect during treatment[22].

In the study by McGowan et al., multiple barriers to treat chronic hepatitis C are described, including the patient's hepatitis C level, presence of comorbidities, lack of awareness of the severity of the disease, and fear of side effects; the low adherence conditions may prevent treatment. In this study, approximately two thirds of the patients reported that the fear of side effects, together with the asymptomatic nature of his/her disease, was the main reason for postponing HCV treatment[22].

Precisely because it causes numerous side effects that impair patients' quality of life, treatment with interferon has stimulated the research and development of alternative treatments for hepatitis C[23].

Currently, new therapies with agents that focus on specific viral proteins, such as protease and polymerase, are emerging. Two protease inhibitors, telaprevir and boceprevir, went through a series of trials and have recently been released. These drugs showed greater efficacy compared to the current therapy (SVR of 60% to 75%), with shorter duration of treatment and without adding side effects to the current treatment, but are restricted to genotype 1 and to recurrent disease treatment[24].

Additionally, these drugs have also shown good efficacy in patients who have failed treatment with interferon combined with RBV (SVR of 60% to 65%)[24].

Another approach to treatment, also aiming to inhibit viral replication, would be the use of oligonucleotides and ribozymes, likewise the subject of experimental investigations. Cytokines, such as interleukins 12, 10, and 2, unlike the abovementioned drugs, would act by modulating the immune system in order to favor the therapeutic response. Also using the same immunotherapy approach, other possibilities are being tested, including the use of a DNA vaccine that, by stimulating a potent T-cell response to the virus, would have a therapeutic purpose. The complexity of the experiments with these new substances results from the near certainty that the best results will derive from a combination of drugs rather than from an isolated drug[25].

Regarding the presence of side effects, no studies that compared the effects generated by the different types of PEG-IFNs were retrieved in the literature.

Conclusion

The study shows a high morbidity related to the treatment, as only 1.2% of the patients presented no side effects.

When comparing the side effects of the two drugs, it can be observed that interferon alpha-2b combined with RBV causes more fever and weight loss when compared to alpha-2a combined with RBV; this relation is statistically significant ($p < 0.05$).

To date, there is no sufficient evidence to indicate one type of PEG-INF over the other and, for this reason, more studies are needed in order to verify whether the results found in this article are replicated in other studies, and if possible, remedy the limitations of this study.

Since the treatment is long, if a drug with less side effects can be prescribed, there will be greater adherence by the patients, which is essential for successfully fighting HCV.

The results of the study will be reported to the healthcare professionals of HEMC, guiding them to better care for patients with hepatitis C, especially those patients subject to treatment with interferon alpha-2b combined with RBV, who will possibly face more exacerbated side effects regarding fever and weight loss.

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