JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Responses to peginterferon alfa-2a vs alfa-2b plus ribavirin in a Mexican population with chronic hepatitis C

Jorge Luis Sandoval-Ramirez[1], José Antonio Mata-Marín[1], Gloria Huerta-García[2], Jesus Enrique Gaytán-Martínez[1]

[1] *Departamento de Infectología adultos. Hospital de Infectología, Centro Médico Nacional "La Raza", Distrito Federal, México*
[2] *Departamento de Infectología Pediátrica. Hospital de Pediatría, Centro Médico Nacional Siglo XXI, Distrito Federal, México*

Abstract

Introduction: The WHO estimates that 180 million people are chronically infected with hepatitis C virus (HCV) throughout the world. Despite the emergence of new therapies, the combination of pegylated interferon and ribavirin remains the accepted standard of care in low-income countries, including Mexico. Two types of peginterferon are available (peginterferon alfa-2a and peginterferon alfa-2b), and both are recommended for the treatment of HCV, although there is controversy over which treatment option is most effective.

Methodology: This was a retrospective cohort study at a infectious disease center in Mexico City. Patients were included if they had received peginterferon alfa-2a or peginterferon alfa-2b plus ribavirin. Age, sex, body mass index, AST platelet ratio index, HCV RNA viral load, levels of alanine aminotransferase, aspartate aminotransferase, bilirubin, albumin, and hemoglobin, and platelet and leukocyte counts of the subjects were assessed before treatment and at weeks 4, 12, 24, 48, and 6 months post treatment.

Results: Eighty-seven patients met the inclusion criteria. A sustained virological response (SVR) occurred in 33 (38%) of them, 11 (33%) given peginterferon alfa-2a and 22 (67%) given peginterferon alfa-2b (p = 0.17). Seventeen patients (20%) relapsed, 7 (41%) of those given peginterferon alfa-2a and 10 (59%) of those given peginterferon alfa-2b (p = 0.76); 27 (31%) patients were non-responders (p = 0.09). The rates of anemia, thrombocytopenia, and leukopenia were similar in both groups.

Conclusions: Similar SVR rates and frequencies of adverse events were observed. Either type of interferon can be used to treat HCV infection in the Mexican population

Key words: genotype 1; treatment; sustained virological response; anemia; relapse.

J Infect Dev Ctries 2015; 9(3):267-273. doi:10.3855/jidc.5284

(Received 12 May 2014 – Accepted 22 December 2014)

Introduction

The World Health Organization estimates that 180 million people are chronically infected with hepatitis C virus (HCV) throughout the world [1]. Up to 85% of HCV-infected individuals go on to develop chronic hepatitis C (CHC), which carries risks of progression to cirrhosis, end-stage liver disease, and hepatocellular carcinoma [2]. During the natural course of CHC, the spontaneous eradication of HCV infection occurs extremely rarely [3]. Despite the emergence of new therapies, the combination of pegylated interferon alfa (peginterferon) and ribavirin remains the accepted standard of care (SOC) in Mexico. The primary goal of HCV therapy is to cure the infection by eliminating detectable circulating HCV after the cessation of treatment [4]. Two types of peginterferon are available – peginterferon alfa-2a and peginterferon alfa-2b – and both are recommended for the treatment of HCV, although there is controversy over which treatment option is the most effective [5,6]. Well-known factors that affect the response to treatment include baseline characteristics such as the HCV genotype, HCV RNA viral load, age, and the degree of fibrosis [7]. In patients infected with HCV genotype 1, the sustained virological response (SVR) rates after the accepted SOC are around 40% worldwide [8].

The prevalence of HCV infection in Mexico is 1.4% (700,000 individuals), and the main genotype is 1 [9]. There is evidence of a more aggressive CHC course in Latin American patients who have higher serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin, lower albumin levels and higher portal inflammation scores in liver biopsies. The available information suggests that there is more rapid progression of liver

disease because of the low efficacy of current therapies [10].

A few studies have compared the effectiveness and safety of peginterferon alfa-2a and alfa-2b, but all have used different statistical designs and the results are inconclusive [2,5,6,8]. However, clinical trials provide a high level of medical and supportive care, which tends to maximize patient compliance, and the inclusion and exclusion criteria may not reflect the clinical picture in a real-life setting [11]. Thus, the main objective of this study was to conduct a "real-life" comparison of peginterferon alfa-2a versus alfa-2b plus ribavirin in a Mexican population with HCV genotype 1.

Methodology

Study design

A retrospective cohort study was conducted at a single infectious disease center in Mexico City, approved by the local ethical committee with reference number R-2013-35021-6. Patients who were older than 16 years with HCV genotype 1 infection and a detectable HCV RNA viral load were enrolled. Patients were included if they had received treatment with peginterferon alfa-2a or peginterferon alfa-2b plus ribavirin between December 2008 and December 2012 at the Hospital de Infectologia La Raza National Medical Center in Mexico City. Complete records were collected, including hematological and biochemical data. Patients who were coinfected with human immunodeficiency virus (HIV) or hepatitis B virus (HBV) were excluded.

Patients and measurements

Patients' age, sex, body mass index, hepatic fibrosis AST–platelet ratio index (APRI) score, HCV RNA viral load, levels of ALT, AST, bilirubin, albumin, and hemoglobin, and platelet and leukocyte counts were assessed. These were measured before the first peginterferon dose and at weeks 4, 12, 24, 48, and 72 (in patients with a delayed virological response), and at 6 months post treatment. The response rates were classified as a rapid virological response (RVR), early virological response (EVR), and SVR. Any adverse hematological events at weeks 4, 12, and 24, and at the end of the treatment were recorded. The end-of-treatment response and SVR were defined as a negative quantitative HCV RNA level at the end of treatment and after 24 weeks in an untreated follow-up, respectively. An EVR was defined as a quantitative HCV RNA-negative (complete EVR) or a reduction from the baseline HCV RNA level of < 2 $\log_{10}$ IU/mL at week 12 (partial EVR). All patients with detectable HCV RNA at week 24 stopped treatment and were classified as nonresponders. Virological relapse was defined as reversion to HCV RNA-positive status in a patient who had an undetectable HCV RNA level (< 43 IU/mL) at the end of the treatment.

Adverse events and dose reductions

Anemia was defined as a hemoglobin level of < 12 g/dL for women and < 13 g/dL for men. Thrombocytopenia was defined as a platelet count of < 50,000 platelets/dL. Leukopenia was defined as a leukocyte count of < 4,000 cells/dL, and neutropenia as a neutrophil count of < 1,000 cells/dL. The dose of peginterferon alfa-2a was reduced from 180 to 135 μg/week and then to 90 μg/week. The dose of peginterferon alfa-2b was reduced from 1.5 to 1.0 μg/kg/week and then to 0.5 μg/kg/week if the absolute neutrophil count decreased to < 750/mm^3 or if the platelet count decreased to < 50,000/mm^3. Treatment was stopped if the neutrophil or platelet count decreased to < 500/mm^3 or < 25,000/mm^3, respectively. The dose of ribavirin was reduced by 200 mg/week if the hemoglobin level decreased to < 10 g/dL, and ribavirin was stopped if the hemoglobin level decreased to < 8.5 g/dL [4].

Statistical analysis

The statistical analysis was based on the median and interquartile range (IQR, 25th to 75th percentile range). A χ^2 test was used to compare categorical variables. Multivariable logistic stepwise regression analysis was used to explore the independent effects of the treatment and the baseline factors (age, body weight, body mass index, sex, presence of cirrhosis, ALT level, HCV RNA level, and HCV genotype) on the likelihood of achieving an SVR. All tests were two sided, and $p < 0.05$ was considered to be significant. The tests were conducted using SPSS software version 20.

Results

A total of 199 records of patients with HCV infection who received treatment were reviewed. Of these, 87 patients met the inclusion criteria; the others were treatment-experienced patients. The median age was 50 years (IQR, 42–59), and 52 (60%) patients were women. Forty-six (53%) patients had subtype 1b. The other baseline data are included in Table 1. Thirty-seven (43%) patients received treatment with

peginterferon alfa-2a, and 50 (57%) patients received peginterferon alfa-2b (Table 1).

Virological response

Thirty-seven patients received treatment for 48 weeks, 11 patients for 72 weeks because of a delayed viral response, and 18 patients stopped treatment in week 12: two because of adverse events and 16 because of a null response. Ten patients were partial responders. An SVR at week 24 (SVR24) occurred in 33 (37%) of these patients: 11 (33%) given peginterferon alfa-2a and 22 (67%) given peginterferon alfa-2b (p = 0.17). An RVR occurred in 17 patients, and 56 (64%) patients achieved an EVR (Figure 1). Of the patients who lacked an SVR24 (n = 54), 17 (31%) relapsed: 7 (41%) given peginterferon alfa-2a and 10 (59%) given peginterferon alfa-2b (p = 0.76). Twenty-seven (31%) patients were nonresponders (p = 0.09, peginterferon alfa-2a vs alfa-2b) (Table 2). Five patients received shortened treatment by 24 weeks (baseline viral load < 800,000 IU/mL, low-level fibrosis indicated by the APRI score, and an RVR); all of these patients had an SVR24.

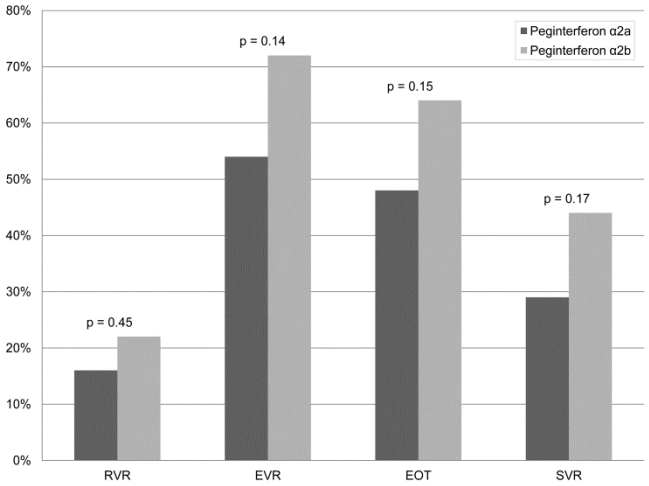
The predictive factors associated with an SVR were evaluated. To identify the independent factors, multivariable logistic regression analysis was used. Only age < 40 years, RVR, and EVR were significantly associated with an SVR (Table 3).

Table 1. Baseline characteristics (n = 87)

	Peginterferon alfa-2a (n = 37)	**Peginterferon alfa-2b (n = 50)**
General		
Men	11 (70.3%)	25 (50%)
Women	26 (29.7%)	26 (50%)
Age (years)	51 (IQR, 42–61)	49 (IQR, 39–57)
Year of diagnosis	2010 (IQR, 2009–2011)	2010 (IQR, 2009–2011)
Subtype		
1a	16 (43%)	22 (44%)
1b	20 (54%)	26 (52%)
Nontypified	1 (3%)	2 (4%)
Mean duration of therapy		
12 weeks	11 (30%)	8 (16%)
24 weeks	10 (27%)	11 (22%)
48 weeks	12 (32%)	25 (50%)
72 weeks	4 (11%)	6 (12%)
APRI		
> 1.2	16 (31.4%)	19 (37.3%)
Body mass index		
Normal	11 (32.4%)	27 (54%)
Overweight	19 (55.9%)	13 (26%)
Obese	4 (11.8%)	10 (20%)
Median HCV RNA		
(UI/mL)	668,000 (IQR, 217,018–1,560,000)	569,000 (IQR, 143,000–1,750,000)
HCV RNA		
< 5.9 log	22 (59.5%)	30 (60%)
> 5.9 log	15 (40.5%)	20 (40%)
Complete blood count		
Hemoglobin (g/dL)	14.8	15.1 (IQR, 14–16)
Platelets	157,000 (IQR, 106,500–211,500)	183,000 (IQR, 121,000–283,000)
Leukocytes	5,540 (IQR, 4,68 –6,120)	5,420 (IQR, 4,600–6,480)
Neutrophils	2,540 (IQR, 1,996–3,377)	2,718 (IQR, 2,368–3,272)
Liver tests		
AST (UI/mL)	74 (IQR, 44–101)	54 (IQR, 30–108)
ALT (UI/mL)	72 (IQR, 49.5–101)	60 (IQR, 41–110)
Total bilirubin (mg/dL)	0.86 (IQR, 0.71–1.35)	0.76 (IQR, 0.51–1.19)
Albumin (g/dL)	4 (IQR, 3.6–4.2)	4 (IQR, 3.8–4.3)

IQR: interquartile range

Figure 1. Response to treatment with peginterferon alfa-2a and alfa-2b



EOT: end-of-treatment response; EVR: early virological response; RVR: rapid virological response; SVR: sustained virological response

Table 2. Virological response during treatment

	Peginterferon alfa-2a (n = 37)	**Peginterferon alfa-2b (n = 50)**	**P value**
RVR	6/17 (35%)	11/17 (65%)	0.45
EVR	20/56 (36%)	36/56 (64%)	0.14
EOT	18/50 (36%)	32/50 (64%)	0.15
SVR	11/33 (33%)	22/33 (67%)	0.17
Relapse	7/17 (41%)	10/17 (59%)	0.90
Null response	9/17 (53%)	8/17 (47%)	
Partial response	5/10 (50%)	5/10 (50%)	
Total nonresponse	14/37 (38%)	13/50 (26%)	0.83
Rebound	2/37 (5%)	2/50 (4%)	NA
Treatment suspended	3/37 (8%)	3/50 (6%)	NA

CI: confidence interval; EOT: end-of-treatment response; EVR: early virological response; NA: not available; RVR: rapid virological response; SVR: sustained virological response

Table 3. Predictive factors associated with SRV

Univariable analyses	**OR**	**P**
Female sex	1.036 (0.597–1.797)	0.901
Age < 40 years	3.357 (1.146–9.813)	**0.023**
APRI < 1.2	1.624 (0.884–2.981)	0.101
Proper weight	1.357 (0.567–3.247)	0.492
RNA VHC < 800,000	1.346 (0.751–2.412)	0.305
Altered liver test	1.429 (0.399–5.113)	0.582
GT1b	1.056 (0.617–1.807)	0.843
RVR	12.526 (3.235–48.496)	**< 0.001**
ERV	6.756 (2.557–17.850)	**< 0.001**
Hb < 12 week 12	1.610 (0.880–2.945)	0.105
Hb < 12 week 24	1.696 (0.880–3.267)	0.078
Hb < 12 week 48	1.610 (0.880–2.945)	0.105
Multivariate analysis		
Age < 40 years	3.268 (0.896–11.916)	0.073
RVR	8.657 (1.77–42.325)	0.008
ERV	3.933 (1.251–12.359)	0.018

EVR: early virological response; RVR: rapid virological response; SVR: sustained virological response; OR: odds ratio

Adverse events

Treatment was suspended for six patients because of adverse events: four because of rash, one because of anemia, and one because of hepatic encephalopathy. The major adverse hematological effects are shown in Table 4.

Discussion

Mexico is a developing country, and the economic resources devoted to health care are limited. Around 90% of patients with VHC are treated in government hospitals and do not have access to direct antiviral agents. In Mexico, treatment with pegylated interferon alfa plus ribavirin remains the only option for almost all of the population.

In this study, we confirmed the same response rate to either of the pegylated interferons used to treat HCV genotype 1 infections in this Mexican population. Similar to Rodriguez-Torres *et al*., who in 2009 reported an SVR rate of 34% in a Latino population compared with an SVR of 49% in a non-Latino population, we found an SVR rate of 37.9% [12]. The IDEAL study by McHutchison *et al*. reported similar SVR rates of 40.9% (95% confidence interval [CI], 37.9–43.9) with peginterferon alfa-2a and 39.8% (95% CI, 36.8–42.8) with peginterferon alfa-2b (p = 0.57) [8]. In 2011, Zurwiesch *et al*. studied a German cohort of 486 patients and reported no significant difference in the SVR rates with peginterferon alfa-2a (53.4%) and alfa-2b (53.7%) [11]. However, some authors have reported better responses with peginterferon alfa-2a. In 2010, Ascione *et al*. reported a prospective single-center, open-label randomized trial (n = 320), which showed that 54.8% of patients treated with peginterferon alfa-2a had an SVR compared with 39.8% of patients treated with peginterferon alfa-2b (95% CI, 0.72–28.5; p = 0.040) [5]. Similar results were reported by Rumi *et al*. in a single-center, open-label randomized trial, which found response rates of 48% in patients who received peginterferon alfa-2a (n = 212) and 32% in patients who received peginterferon alfa-2b (n = 219) (p = 0.04) [13]. Berak *et al*. found no differences in SVR or relapse rates between the two interferons in the treatment for HCV in a Spanish cohort. They suggested that the advantage of interferon alfa 2b is that it makes continuation of therapy for > 12 weeks unnecessary for patients who are unlikely to respond [14].

We evaluated factors that may be related to the treatment response, such as RVR, EVR, age, sex, hepatic fibrosis (APRI score), RNA HCV viral load, obesity, and AST level. The stepwise logistic regression model identified only three factors as being independently related to an SVR in the two groups: age < 40 years, RVR, and EVR.

McHutchison *et al*. found that age < 40 years, basal HCV RNA level < 400,000 IU/mL, fibrosis, and RVR or EVR were predictors of an SVR. Our univariate analysis showed that age < 40 years, HCV

Table 4. Adverse hematological events

Adverse event	Peginterferon alfa-2a	Peginterferon alfa-2b	P value
Week	**Anemia (hemoglobin < 12 women/ < 13 men)**		
4	13 (15.10%)	16 (18.6%)	0.65
12	21 (24.70%)	29 (34.11%)	0.85
24	18 (26.86%)	28 (41.79%)	0.93
48	11 (23.40%)	16 (34.04%)	0.26
Week	**Platelets (< 50,000/mL)**		
4	2 (2.32%)	3 (3.48%)	0.93
12	5 (5.88%)	2 (2.35%)	0.9
24	2 (2.98%)	1 (1.49%)	0.31
48	1 (2.12%)	1 (2.12%)	0.62
Week	**Leukopenia (< 4,000 leucocytes)**		
4	20 (23.35%)	31 (36.04%)	0.54
12	23 (27.38%)	34 (40.47%)	0.97
24	17 (25.37%)	27 (40.29%)	0.96
48	12 (25.53%)	18 (38.29%)	0.25
Week	**Neutropenia (< 1,000 neutrophils/mL)**		
4	8 (9.30%)	10 (8.6%)	0.8
12	7 (8.33%)	11 (13.09%)	0.87
24	5 (7.46%)	5 (7.46%)	0.43
48	4 (8.51%)	5 (10.63%)	0.46

RNA viral load < 400,000 IU/mL, RVR, and EVR were predictors of an SVR, but the only factors that remained significant in the multivariate analysis were age < 40 years, RVR, and EVR.

There was no difference in the rate of adverse hematological events between the two treatment groups.

The rate of relapses was 19% in the present study and did not differ between the two groups. By contrast, Ascione *et al*. reported a significant difference in relapse rates: 20.4% with peginterferon alfa-2a and 9.7% with peginterferon alfa-2b (95% CI, 0.38–21.2; p = 0.040) [5]. In the IDEAL study, McHutchison *et al*. reported relapse rates of 31.5% for peginterferon alfa-2a and 23.5% for alfa-2b, although these did not differ significantly [8]. In 2009, Rodríguez Torres *et al*. reported relapse rates of 36% in Latin-American patients compared with 26% in a non-Latino population [12]. They also showed that in the Latin-American population, greater weight and obesity were significantly related to the SVR; 65% of the treated patients in their study had a body mass index of > 27 kg/m^2. In our study, 52% of patients were overweight. We had expected that being overweight would be related to the SVR rates, but our sample size was small to support any difference related to body weight. In addition, we could not assess insulin resistance, which is also associated with a worse prognosis in Latin American patients.

The present study was a real-life comparison of the two accepted pegylated interferons used to treat infections with HCV genotype 1 and is the first of its kind in a Mexican population. All patients were ambulatory and learned how to administer the peginterferon themselves or were aided by a close relative, so our study gave an insight into how the drug works in a real-life population. Most of our population does not have access to the new antiviral drugs and therefore must continue using pegylated interferon and ribavirin. Our study shows that either of the pegylated interferons is a good option for this population. The main weaknesses of our study are that it was a cohort design and that we worked with medical records, and thus we lacked data such as information about psychiatric events. We could not assess the ribavirin dose adjustment in all patients and could not evaluate the effect of this adjustment on the SVR. Some studies have suggested that a lower dose of ribavirin may affect the SVR in patients treated with peginterferon alfa-2a. The practice in our unit is to try to maintain a ribavirin dosage at > 600 mg every 24 hours. Our center is a tertiary referral hospital, and we included only HCV treatment-naïve infected patients, which is why we had a small sample size. This may have limited the ability of our multivariate analysis to identify more than three predictors of an SVR.

Conclusions

Our results suggest that either of the pegylated interferons can be used to treat HCV infection in the Mexican population. Both interferons should be expected to have similar virological response rates and the same frequencies of adverse events.

Acknowledgements

We thank our study team.

References

1. World Health Organization (2014) Hepatitis C fact sheet. Geneva: World Health Organization. Available: http://www.who.int/mediacentre/factsheets/fs164/en/. Accessed April 2014.
2. Witthoeft T, Hueppe D, John C, Goelz J, Heyne R, Moeller B, Teuber G, Wollschlaeger S, Baumgarten A, Simon KG, Moog G, Dikopoulos N, Mauss S (2010) Efficacy and tolerability of peginterferon alfa-2a or alfa-2b plus ribavirin in the daily routine treatment of patients with chronic hepatitis C in Germany: the PRACTICE study. J Viral Hepat 17: 459-468.
3. Yokosuka O, Kojima H, Imazeki F, Tagawa M, Saisho H, Tamatsukuri S, Omata M (1999) Spontaneous negativation of serum hepatitis C virus RNA is a rare event in type C chronic liver diseases: analysis of HCV RNA in 320 patients who were followed for more than 3 years. J Hepatol 31: 394-399.
4. European Association for the Study of the Liver (2011) EASL Clinical Practice Guidelines. Management of hepatitis C virus infection. J Hepatol 55: 245-264.
5. Ascione A, De Luca M, Tartaglione MT, Lampasi F, Di Costanzo GG, Lanza AG, Picciotto FP, Marino-Marsilia G, Fontanella L, Leandro G (2010) Peginterferon alfa-2a plus ribavirin is more effective than peginterferon alfa-2b plus ribavirin for treating chronic hepatitis C virus infection. Gastroenterology 138: 116-122.
6. Awad T, Thorlund K, Hauser G, Stimac D, Mabrouk M, Gluud C (2010) Peginterferon alpha-2a is associated with higher sustained virological response than peginterferon alfa-2b in chronic hepatitis C: systematic review of randomized trials. Hepatology 51: 1176-1184.
7. Ferenci P (2004) Predictors of response to therapy for chronic hepatitis C. Semin Liver Dis 24 Suppl 2: 25-31.
8. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, Nyberg LM, Lee WM, Ghalib RH, Schiff ER, Galati JS, Bacon BR, Davis MN, Mukhopadhyay P, Koury K, Noviello S, Pedicone LD, Brass CA, Albrecht JK, Sulkowski MS; IDEAL Study Team (2009) Peginterferon alfa-2b or alfa 2a with ribavirin for treatment of hepatitis C infection. N Engl J Med 361: 580-593.
9. Valdespino JL, Conde-González CJ, Olaiz-Fernández G, Palma O, Kershenobich D, Sepúlveda J (2007) Seroprevalence of hepatitis C among Mexican adults: an emerging public health problem? Salud Publica Mex 49 Suppl 3: S395-S403.

10. Rodríguez-Torres M (2008) Latinos and chronic hepatitis C: a singular population. Clin Gastroenterol Hepatol 6: 484-490.
11. Zurwiesch JS, Pudelski N, Hoepner L, Supplieth M, Buggisch, Lohse AW, Lüth S (2011) "Real-life" comparison of pegylated-interferon 2a versus 2b combination therapy of chronic hepatitis C virus. Hepatology 53: 1405-1406.
12. Rodríguez-Torres M, Jeffers LJ, Sheikh MY, Rossaro L, Ankoma-Sey V, Hamzeh FM, Martin P (2009) Peginterferon alfa-2a and ribavirin in Latino and non-Latino whites with hepatitis C. N Engl J Med 360: 257-267.
13. Rumi MG, Aghemo A, Prati GM, D'Ambrosio R, Donato MF, Soffredini R, Del Ninno E, Russo A, Colombo M (2010) Randomized study of peginterferon-α2a plus ribavirin vs peginterferon-α2b plus ribavirin in chronic hepatitis C. Gastroenterology 138: 108-115.
14. Berak H, Laskus T, Kolakowska-Rzadzka A, Wasilewski M, Stanczak JJ, Bardadin K, Walewska-Zielecka B, Horban A (2014) Peginterferon alfa-2a and peginterferon alfa-2b combined with ribavirin in patients with genotype 1 chronic hepatitis C: results of a prospective single-centre study. Adv Med Sci 59: 261-265.

Corresponding author
Jorge Luis Sandoval Ramírez, MD
Servicio de Infectología adultos
Hospital de Infectología Centro Médico Nacional La Raza
Jacarandas Esquina con Seris s/n Colonia La Raza
Distrito Federal CP 23924, México
Phone: + 52-57245900 ext 23924.
Email: escribo_a_jorge@yahoo.com.mx

Conflict of interests: No conflict of interests is declared.