Hematological and dermatological adverse events during hepatitis C treatment with peg-interferon and ribavirin

Eventos adversos hematológicos e dermatológicos durante o tratamento da hepatite C com interferon peguilado e ribavirina

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ABSTRACT

OBJECTIVE: To evaluate frequency and impact of adverse events, mainly the hematological and dermatological ones, on sustained virological response, and compliance to hepatitis C treatment. **METHODS:** Patients were treated according to the guidelines of the Brazilian Ministry of Health. Variables associated with hematological and dermatological adverse events were: age, gender, stage of fibrosis, type of Pegylated interferon, dose reductions, temporary discontinuation and early interruption of treatment. **RESULTS:** Two hundred and twenty two patients were studied (58% females; age 49±11 years). Dose reductions, temporary interruptions, and early discontinuations were observed in 21%, 8% and 9.5% of patients, respectively. The main adverse events were hematological (anemia, neutropenia and thrombocytopenia) and dermatological (pruritus and alopecia). Anemia (Hemoglobin <10g/dL) was associated with female gender (p<0.001), advanced fibrosis (p=0.047) and dose reductions (p<0.001); neutropenia with advanced fibrosis (p=0.003) and temporary discontinuation (p=0.002); thrombocytopenia with advanced fibrosis (p<0.001) and pegylated interferon α2a (p=0.05). Pruritus and alopecia were associated to female gender (p=0.008 and p=0.02) and treatment interruption (p=0.029 and p=0.02). **CONCLUSION:** Hematological and dermatological adverse events are frequent in hepatitis C patients treated with pegylated interferon and ribavirin. However, despite frequent dose reductions and interruptions, these adverse events did not affect the sustained virological response.

Key-words: Hepatitis C/drug therapy; Ribavirin/adverse effects; Interferon-alpha/adverse effects; Anemia/chemically induced; Skin manifestations

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RESUMO

OBJETIVO: Avaliar a frequência e o impacto de eventos adversos, principalmente hematológicos e dermatológicos, na resposta virológica sustentada e na aderência ao tratamento para hepatite C. **MÉTODOS:** Os pacientes foram tratados de acordo com diretriz do Ministério da Saúde. Variáveis associadas com eventos adversos hematológicos e dermatológicos foram: idade, sexo, grau de fibrose, tipo de interferon peguilado, reduções de dose, descontinuação temporária e interrupção precoce do tratamento. **RESULTADOS**: Foram estudados 232 pacientes (58% mulheres; idade 49±11 anos). Reduções de dose, interrupções temporárias e descontinuações precoces foram observadas em 21%, 8% e 9,5% dos pacientes, respectivamente. Os principais eventos adversos foram hematológicos (anemia, neutropenia e plaquetopenia) e dermatológicos (prurido e alopecia). Anemia (hemoglobina <10g/dL) se associou a sexo feminino (p<0,001), fibrose avançada (p=0,047) e reduções de doses (p<0,001); neutropenia com fibrose avançada (p=0,003) e interrupção temporária (p=0,002); plaquetopenia com fibrose avançada (p<0,001) e interferon peguilado α2a (p=0,05). Prurido e alopecia se associaram ao sexo feminino (p=0,008 e p=0,02) e interrupção do tratamento (p=0,029 e p=0,02). **CONCLUSÃO:** Eventos adversos hematológicos e dermatológicos foram frequentes em pacientes tratados com interferon peguilado e ribavirina. Entretanto, a despeito de frequentes reduções de dose e interrupções, estes eventos adversos não afetaram a resposta virológica sustentada.

Descritores: Hepatite C/quimioterapia; Ribavirina/efeitos adversos; Interferon-alfa/efeitos adversos; Anemia/induzido quimicamente; Manifestações cutâneas

INTRODUCTION

Infection with hepatitis C virus (HCV) is a serious public health problem that affects 180 million people worldwide, corresponding to about 3% of the world population.[1] Combination treatment of hepatitis C with pegylated-interferon alpha (PegIFN-α) and ribavirin is effective against HCV but is associated with many adverse events (AE).[2] This combination has been used until 2011, when protease inhibitors were added to the dual regimen.[3] After this introduction, AE became more intense than those observed previously, often with negative repercussions on the health and quality of life of the patients, with the success of treatment[4] being significantly compromised.

The main AE resulting from treatment with PegIFN-α and ribavirin include flu-like syndrome, gastrointestinal disorders, neuropsychiatric symptoms, dermatological manifestations, and hematological abnormalities.[5,6] The two latter events are the most common also in triple therapy, and have the greatest impact on tolerance to treatment. Hematological abnormalities, especially anemia, are associated to treatment with two protease inhibitors (boceprevir and telaprevir), whereas dermatological manifestations such as skin rash are associated with the use of telaprevir.[7]

There are few studies in the literature that have investigated in detail the frequency and nature of these AE during dual therapy, AE related to dose reductions, and the association of these events with epidemiological and clinical variables and with sustained virological response (SVR) rates. Most of the data regarding the impact of AE on the success of treatment derive from controlled clinical trials, which do not reflect what happens in the "real world" or at most services where patients are not as carefully selected and not as rigorously followed up. Therefore, the effect of these AE on the response to treatment deserves further investigation and better characterization.

The aims of the present study were to evaluate the frequency of hematological alterations and dermatological manifestations during treatment with PegIFN-α and ribavirin in hepatitis C genotype-1 patients; the relationship of these AE with clinical-epidemiological and histological variables, and the impact of the AE on treatment outcomes: dose reduction, temporary or definitive discontinuation of therapy, and treatment response.

METHODS

Patients chronically infected with HCV genotype 1, followed up at the Hepatitis outpatient clinic of the Department of Gastroenterology, at Universidade Federal de São Paulo between 2002 and 2010, were studied.

The study was approved by the local Ethics Committee and all patients signed the informed consent to participate.

Study design

Patients with chronic hepatitis C infected with HCV genotype 1, and treated with PegIFN-α plus ribavirin between 2002 and 2010 were eligible for the study. The patients were studied retrospectively through the analysis of standardized records for treatment monitoring and recording of AE.

Patients with the following conditions were excluded: co-infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV), autoimmune liver disease, abusive alcohol consumption (>50g ethanol/day), chronic renal failure, and organ transplant. Records that did not contain clear safety information were disregarded.

Laboratory diagnosis

HCV infection was diagnosed by serological and virological tests. Patients infected with HCV were positive for anti-HCV antibodies and HCV RNA.

For serological testing, anti-HCV antibodies were detected by a third-generation enzyme-linked immunosorbent assay (ELISA) (Abbott Laboratories, Chicago, IL, USA), which uses antigens of the core, NS3 and NS4 regions, according to manufacturer's instructions.

For virological analysis, the presence of HCV RNA was investigated before treatment, during months 1, 3 and 12 of treatment, and 6 months after treatment by RT-PCR using commercial kits (Amplicor™, Roche Molecular Systems, Pleasanton, CA, USA). The lower limit of detection of the method was 50IU/mL. The HCV RNA genotype was identified by amplification and hybridization (INNo-LiPA HCV II, Innogenetics NV, Belgium).

Histological diagnosis

Tissue fragments obtained from a liver biopsy were evaluated regarding the stage of fibrosis (F) using the Metavir system,[8] which classifies liver fibrosis from grade 0 to 4. For comparative analysis, fibrosis was classified into less advanced stages, characterized by the absence of septa (F0-2), and more advanced stages, characterized by the presence of fibrous septa or cirrhosis (F3-4).

Treatment regimen

Patients were treated according to the guidelines of the Brazilian Ministry of Health,[9] which recommended a combination treatment with PegIFN-α and ribavirin for 48 weeks for patients infected with HCV genotype 1.

The rate of SVR was evaluated in all patients who used at least one dose of the prescribed medication (intention-to-treat analysis).

Analysis of adverse events

Hematological events

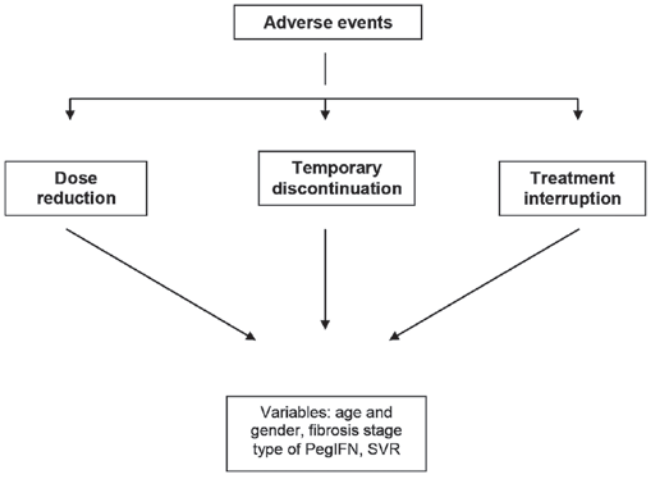
Serum levels of hemoglobin (Hb), leukocytes and platelets were determined for analysis of the following AE: anemia (Hb≤10g/dL), leukopenia (≤1,500/mm^3), and thrombocytopenia (≤50,000/mm^3). These parameters were evaluated before treatment and at 1, 3, 6 and 12 months of antiviral therapy.

Dermatological events

Dermatological alterations were analyzed throughout the period of treatment. These data were recorded on standardized treatment and AE monitoring forms.

Comparative analysis

The following outcomes that are secondary to AE were considered for comparative analysis: reduction in PegIFN-α and/or ribavirin dose due to hematological and/or dermatological alterations, temporary discontinuation of therapy (discontinuation of PegIFN-α and/or ribavirin for a maximum of 2 weeks and restart of the medications thereafter) due to hematological and/or dermatological alterations, and definitive interruption of therapy due to hematological and/or dermatological alterations (Figure 1).



PegIFN: pegylated interferon; SVR: sustained virological response.

Figure 1. Outcomes secondary to hematological and/or dermatological adverse events.

The association between the occurrence of these events and the following variables was analyzed: age, gender, stage of fibrosis, type of interferon used (PegIFN-α 2a and 2b), and SVR.

Statistical analysis

The numerical variables are expressed as the mean, median and standard deviation. The qualitative variables were compared by theC-squared test or Fisher's exact, when appropriate. A level of significance of 0.05 (a=5%) was adopted. Descriptive levels below this value were considered to be significant. Statistical analysis was performed using the SPSS for Windows software, version 17 (SPSS, Chicago, IL, USA).

RESULTS

A total of 232 patients with genotype 1 chronic hepatitis C treated with PegIFN and ribavirin was studied. Of these, 135 (58%) were females and 97 (42%) were males. Age ranged from 20 to 71 years (mean: 49±11 years). Histological analysis showed that 31% of the patients had advanced fibrosis (F3-4) (Table 1) and 153 (66%) were treated with PegIFN-α 2b.

Hematological adverse events

Hematological abnormalities during treatment were observed in more than half of the patients. Anemia (Hb≤10g/dL) was the most frequent laboratory alteration (30% of patients). Table 2 shows the hematological abnormalities during treatment.

Dermatological adverse events

Dermatological AE were observed in 171/232 (74%) patients who started treatment with PegIFN and ribavirin. Pruritus was the most frequent dermatological symptom (Figure 2).

Table 1. Clinical and histological characteristics of the patients with genotype 1 hepatitis C treated with pegylated interferon (PegIFN) and ribavirin (n=232)

Characteristics	n (%)
Age (years)	49±11
Gender	
Male	97 (42)
Female	135 (58)
Fibrosis	
F 0-2	158 (69)
F 3-4	72 (31)
Type of PegIFN	
α2a	79 (34)
α2b	153 (66)
SVR	
Yes	102 (45)
No	124 (55)

SVR: sustained virological response.

Table 2. Hematological abnormalities observed in the population studied (n=232)

Laboratory abnormalities	n (%)
Hemoglobin ≤10g/dL	69 (29.7)
Leukocytes ≤1,500/mm^3	24 (10.3)
Platelets ≤50,000/mm^3	18 (7.8)

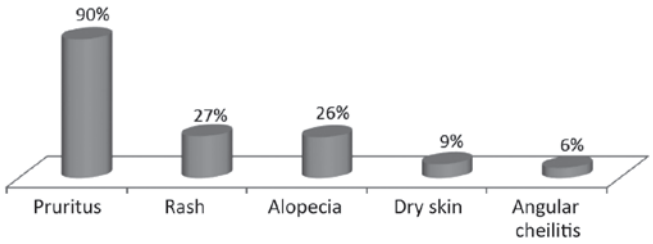


Figure 2. Distribution of the main dermatological manifestations found in the group studied (N=171).

Impact of hematological and dermatological adverse events on dual therapy with PegIFN-α and ribavirin

Forty-seven patients required dose reduction due to hematological and dermatological AE. Of these, 45 patients reduced the PegIFN-α and/or ribavirin dose due to hematological alterations and two patients due to dermatological alterations.

Temporary discontinuation of dual antiviral therapy due to hematological and dermatological AE was observed in 11 patients. Of these, 10 patients discontinued PegIFN-α and/or ribavirin due to hematological alterations and one patient due to dermatological alterations.

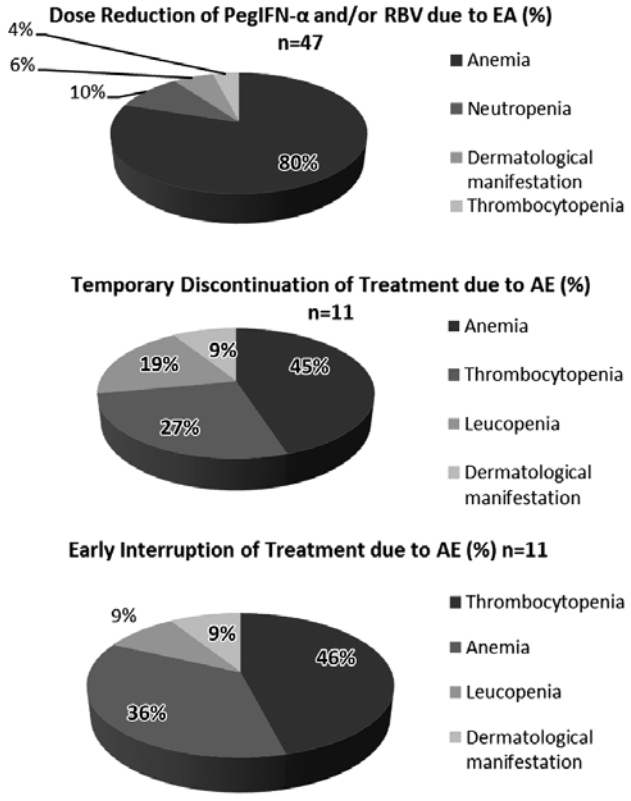
Eleven patients required early interruption of treatment due to hematological and dermatological AE, with 10 patients interrupting treatment permanently due to hematological alterations and one patient due to dermatological alterations.

The main dermatological and hematological manifestations that led to dose reductions, temporary discontinuation of therapy and treatment interruption are shown in Figure 3.

Comparative analysis between dermatological and hematological manifestations resulting from treatment with PegIFN and ribavirin and demographic, histological and treatment variables

In the population studied, the occurrence of anemia was associated with female gender (p<0.001), advanced fibrosis (p=0.047), and a reduction in the PegIFN-α and/or ribavirin dose (p<0.001); leukopenia was associated with advanced fibrosis (p=0.003) and temporary discontinuation of PegIFN-α and/or ribavirin (p=0.002); and thrombocytopenia was associated with advanced fibrosis (p<0.001, Chi-squared) and the type of PegIFN (p=0.05) (Table 3).

A significant association was observed between pruritus and female gender (p=0.008) and treatment interruption (p=0.029); alopecia was associated with female gender (p=0.022), treatment interruption (p=0.016) and dose reduction of PegIFN and/or RBV (p=0.025) (Table 4).



PegIFN: pegylated interferon; RBV: ribavirin; AE: adverse events.

Figure 3. Adverse events that resulted in dose reduction, temporary discontinuation, or early interruption of antiviral therapy in the group studied.

DISCUSSION

The success of treatment of chronic hepatitis C with PegIFN-α and ribavirin depends on good treatment compliance, which is important to obtain SVR. However, in view of the large number of AE, many patients eventually do not adhere adequately to treatment, interrupting therapy early or requiring dose adjustments or temporary discontinuation of the medications.[2]

This study specifically evaluated hematological and dermatological manifestations in 232 patients infected with HCV genotype 1. These are the most common and most striking AE in dual antiviral therapy after flu-like syndrome that occurs in almost all patients and is more easily handled with symptomatic treatment.[2] Furthermore, these AE are the most frequently observed in triple therapy, which is currently used for patients infected with genotype 1.[10] Thus, knowledge of the frequency of occurrence of these events during dual therapy is important in order to allow the correct identification of the implicated drug. It was also the aim of this study to understand the impact of these EAs on the response to treatment (SVR).

The rate of SVR observed in this study was 45%, in accordance with clinical trials register of PegIFN associated to ribavirin for the treatment of hepatitis C. Manns et al.[5] reported 45% of SVR in patients with genotype 1 treated with PegIFN, and Fried et al.[6] found 42% of SVR in genotype 1 patients treated with PegIFN.

AE occur almost universally in hepatitis C patients treated with PegIFN-α and RBV and could affect all organs and systems.[2] In registration trials[5,6] the rate of discontinuation of therapy due to AE was 10-14%. With the introduction of currently used new agents to treat hepatitis C, such as boceprevir and telaprevir, these AE became more intense and more frequent. Among these events, hematological and dermatological abnormalities are also the most frequently reported.[10]

In the present study, dose reductions, temporary discontinuation and early interruption of treatment due to hematological and dermatological AE occurred in 47/232 (20%), 11/232 (5%) and 11/232 (5%) patients, respectively. Hematological alterations had the greatest impact on therapy, being responsible for 94% of dose reductions as well as 91% of the temporary discontinuations and early interruptions of treatment. The dermatological manifestations, although more frequent, had less impact on adherence, contributing to 6% of dose reduction, 9% of temporary discontinuation, and 9% of early interruption.

Anemia, neutropenia and thrombocytopenia are frequent hematological abnormalities that interfere with treatment compliance.[11] Anemia is primarily caused by the accumulation of ribavirin metabolites in erythrocytes, resulting in extravascular hemolysis, and secondarily by the suppression of erythropoiesis in bone marrow mediated by interferon. Neutropenia and thrombocytopenia are also a consequence of this bone marrow suppression.

In the present study, more than half of the patients had Hb levels lower than 10g/dL. These results show that a decline in

Table 3. Occurrence of hematological alterations versus demographic, histological and treatment variables in the population studied (n=232)

Variable	Anemia (n=69)		Leukopenia (n=24)		Thrombocytopenia (n=18)	
	n (%)	p-value	n (%)	p-value	n (%)	p-value
Gender						
Female	54 (78)	**<0.001**	14 (58)	0.988	12 (67)	0.151
Male	15 (22)		10 (42)		6 (33)	
Age						
>40	59 (85)	0.089	20 (83)	0.539	17 (94)	0.373
<40	10 (15)		4 (17)		1 (6)	
Fibrosis						
Grade 3-4	27 (39)	**0.047**	15 (63)	**0.003**	13 (72)	**<0.001**
Grade 0-2	42 (61)		9 (37)		5 (28)	
SVR						
Yes	35 (51)	0.407	10 (42)	0.718	5 (28)	0.078
No	34 (49)		14 (58)		13 (72)	
PegIFN						
2b	41 (63)	0.610	11 (52)	0.180	9 (53)	**0.050**
2a	24 (37)		10 (48)		8 (47)	
Treatment interruption						
Yes	7 (10)	0.823	3 (12)	0.594	6 (33)	0.677
No	62 (90)		21 (88)		12 (67)	
Dose discontinuation						
Yes	7 (10)	0.480	6 (25)	**0.002**	5 (28)	0.733
No	62 (90)		18 (75)		13 (72)	
Dose reduction						
Yes	30 (43)	**<0.001**	6 (25)	0.623	3 (17)	0.207
No	39 (57)		18 (75)		15 (83)	

SVR: sustained virological response; PegIFN: pegylated interferon. Statistically significant associations in bold.

Table 4. Occurrence of dermatological alterations versus demographic, histological and treatment variables in the population studied (N=232)

Variable	Pruritus (n=154)		Rash (n=44)		Alopecia (n=45)	
	n (%)	p	n (%)	p	n (%)	p
Gender						
Female	90 (58)	**0.008**	16 (36)	0.955	27 (60)	**0.022**
Male	64 (42)		28 (64)		18 (40)	
Age						
>40	119 (77)	0.281	32 (73)	0.159	34 (76)	0.353
<40	35 (23)		12 (27)		11 (24)	
Fibrosis						
Grade 3-4	62 (41)	0.861	22 (50)	0.503	24 (53)	0.935
Grade 0-2	91 (59)		22 (50)		21 (47)	
SVR						
Yes	69 (46)	0.134	16 (37)	0.808	21 (50)	0.817
No	80 (54)		27 (63)		21 (50)	
PegIFN						
2b	90 (63)	0.661	33 (79)	0.741	27 (68)	0.204
2a	54 (37)		9 (21)		13 (32)	
Treatment interruption						
Yes	15 (10)	**0.029**	8 (18)	0.660	2 (4)	**0.016**
No	139 (90)		36 (82)		43 (96)	
Dose discontinuation						
Yes	15 (10)	0.186	6 (14)	0.422	2 (4)	0.849
No	139 (90)		38 (86)		43 (96)	
Dose reduction						
Yes	28 (18)	0.062	5 (11)	0.624	9 (20)	**0.025**
No	126 (82)		39 (89)		36 (80)	

SVR: sustained virological response; PegIFN: pegylated interferon. Statistically significant associations in bold.

Hb during treatment is frequent and intense. Manns et al.[5] observed a reduction in Hb to levels below 10g/dL in 9% of cases, whereas this rate was 29% in the present study. This marked difference in anemia cases might be explained by the presence of a larger number of women in the sample studied here. Indeed, this study showed a relationship of anemia with female gender, advanced fibrosis and a reduction in the PegIFN and/or ribavirin dose. This finding is expected since women, in addition to losing blood during the menstrual period, usually receive a higher dose of ribavirin compared to men per kilogram of body weight, leading to a higher incidence of this AE. Other studies have also shown that women have a higher incidence of anemia when compared to men.[11,12]

Neutropenia, which occurs mainly in the first two weeks of treatment, was observed in 6.5% of the patients (granulocytes ≤500/mm^3). In the study of Koskinas et al.,[13] 16% of patients presented neutropenia below 800/mm^3. In the study of Fried et al.[6] three patients that were receiving PegIFN-α 2a and RBV (n=453) and one patient receiving PegIFN-α 2b and RBV (n=444) prematurely discontinued treatment due to neutrophil counts below 500/mm^3. In our study, the occurrence of leukopenia was associated with a more advanced stage of fibrosis (F3-4) and with temporary discontinuation of PegIFN and/or ribavirin. More intense stages of fibrosis sometimes are associated with portal hypertension, leading to leukocytes and platelets reduction due to hyperesplenism.

Cases of thrombocytopenia of less than 50,000 platelets/mm^3 are uncommon. In the present study, only 8% of the patients had severe thrombocytopenia. Huang et al.[14] observed platelet counts of less than 50,000/mm^3 in 17% of patients older than 65 years, and in 13% of patients aged 50 to 64 years. Similar to neutropenia, thrombocytopenia was also associated with advanced fibrosis and, consequently, to temporary discontinuation of the antiviral therapy. Additionally, thrombocytopenia was associated with the type of PegIFN administered. Patients treated with PegIFN-α 2a had a higher rate of thrombocytopenia when compared with patients treated with PegIFN-α 2b. In the study of Fried et al.[6] four patients treated with PegIFN-α 2a and RBV (n=453) and 1 patient treated with PegIFN-α 2b and ribavirina (n=444) had to discontinue treatment due to plaquetopenia.

Dermatological AE seem to be more related to ribavirin and disappear within a few weeks after discontinuation of this medication.[15] In the present study, 171/232 patients (76%) receiving dual antiviral therapy had some type of dermatological manifestation. Among the 171 patients with dermatological manifestations, pruritus occurred in 153/171 (90%), and skin rash and alopecia in 27% and 26%, respectively. In the study of Manns et al.,[5] alopecia was the most common dermatological manifestation (36%), followed by pruritus (29%). The higher incidence of pruritus observed in the present study is probably related to the more intense solar exposure in a tropical country, which contributes to intensify this symptom in patients exposed to drugs known to be related to pruritus, such as ribavirin. Regarding alopecia, in the study conducted by Huang et al.,[14] this symptom was observed in 36% of patients, a higher incidence than that of the present study. Probably this fact is related to the older age of the patients included in that study.

The occurrence of pruritus and alopecia were associated with female gender and treatment interruption. In addition, alopecia was also associated with dose reduction of PegIFN and/or RBV. Dermatological manifestations that lead to any impact in study therapy used to be severe and non-responsive to control treatments, reducing patient's quality of life significantly.

CONCLUSIONS

The present study could demonstrate that hematological and dermatological adverse events are very frequent in patients treated with pegylated-interferon alpha and ribavirin, with anemia showing the highest incidence. These adverse events lead to dose reductions, temporary interruptions, and early discontinuation of treatment. However, these modifications of therapy had no impact on sustained virological response.

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