ORIGINAL PAPER

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Adverse effects of peg-Interferon and Ribavirin combined antiviral treatment in a Romanian hepatitis C virus infected cohort

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Abstract

Introduction: Adverse effects appearing during combined peg-Interferon and Ribavirin antiviral treatment against chronic infection with the hepatitis C virus are a major cause for treatment failures and abrupt interruption. In the prospect of the imminent introduction of new direct acting antiviral agents, with demonstrated higher rates of adverse effects, our study aimed to assess the severity and incidence of several types of adverse effects in a cohort of genotype 1 infected Romanian patients. *Materials and Methods*: We prospectively included a total of 150 patients (45 men), aged 25 to 64 years, who received combined peg-Interferon and Ribavirin antiviral treatment for chronic hepatitis C. Out of these, 145 patients also had liver biopsies prior to treatment initiation. We recorded their viral loads, hemoglobin values and thrombocyte counts, as well as any dermatological, psychiatric or constitutional adverse effect after twelve doses, eight and twelve months of treatment, with two follow-up examinations at three and six months after treatment completion. *Results*: Viral loads significantly decreased after 12 doses of treatment, in the end a total of six patients (two men and four women) being declared non-responders. Hemoglobin values and thrombocyte counts significantly decreased during treatment ($p<0.0001$), with their values being restored to pre-treatment levels during the follow-up period. We did not find significant differences between the 12-doses, 8 and 12 months values during treatment ($p>0.05$). We recorded 43 cases (11 men and 32 women) presenting with rashes, drug eruptions and erythema. We only encountered grade 1 and 2 dermatological adverse effects. Psychiatric effects were present in 34 cases (10 men and 24 women, 22.6% of the group) and manifested as mild depressions, which did not require specific medication or antiviral dose adjustment. Patients also presented headaches (80.6%), fatigue (71.3%), nausea (47.3%), arthralgias (35.3%) and fever (30%). *Conclusions*: We did not encounter severe hematological adverse effects that would require Ribavirin dosage adjustments. Cutaneous and psychiatric adverse effects were also present in a significant number of patients; however, their severity did not influence the continuity or outcome of the antiviral treatment. Other constitutional effects were also present with no direct consequence on the course of treatment. Future agents employed in antiviral therapy shall require extensive monitoring of all adverse effects already acknowledged during dual combination therapy.

***Keywords*:** peg-Interferon, Ribavirin, adverse effects, chronic hepatitis C.

Introduction

A new virus responsible for over 80% of all non-A and non-B hepatitis cases related to blood transfusions was identified and successfully cloned in 1989 [1]. It was named the hepatitis C virus (HCV) and since then was found to consistently infect approximately 2.2–3% of the world population [2, 3]. The latest estimations of the *World Health Organization* are that approximately 130 to 170 million people are chronically infected with HCV [2–4]. The highest prevalence of HCV infection is found in the African and the Eastern Mediterranean regions, with more than 2.5% of the general population currently being infected [2, 3]. Figures for Romania show prevalence of approximately 4.9% [2–5], the majority of infections being attributed to the type 1 HCV genotype (between 93.46% [5] and even 99.13% according to a national multicenter study [6]).

The current standard of care for HCV infections is a combination of pegylated interferon (pegIFN) alpha-2a or alpha-2b and Ribavirin (RBV), with successful viral remission in around 60% of treated cases [7]. Type 1 genotype, such as the one found in the vast majority of HCV-infected Romanians, leads to poorer antiviral response, with approximately 40 to 50% sustained virological responses (SRV) [8, 9]. In the coming years, a number of direct acting antivirals (DAAs) will be added to the standard double therapy currently employed. These NS3/4A protease inhibitors and NS5B polymerase or NS5A inhibitors are expected to raise the number of cured HCV patients to over 75% [10–12].

However, antiviral therapy does not come without risks or unwanted adverse effects (AEs). Effective management of all these AEs improves adherence significantly and reduce the early discontinuation of treatment, thus significantly improving antiviral effects [10]. The most severe AEs of antiviral therapy are caused by both pegIFN and RBV, the addition of DAAs further amplifying their severity and duration [9–12]. The most common AEs are hematological, such as anemia and thrombocytopenia [10–12]; dermatological, most frequently rashes of various degrees and pruritus [10, 13, 14]; psychiatric (depression developed during antiviral treatment is not uncommon) [15–17]; endocrine and anorectal.

The aim of our study was to investigate the frequency

and evolution of AEs in a cohort of patients undergoing double pegIFN alpha-2a and RBV treatment over the course of 48 weeks, also taking into account the initial severity of liver alteration as well as the success of antiviral therapy.

Materials and Methods

We prospectively included 150 patients (45 men, 105 women) between January 2008 and December 2010 in the Emergency County Hospital of Craiova, who started combined pegIFN alpha-2a and RBV treatment for chronic hepatitis C (CHC) for 48 weeks (Table 1). Patients were assessed post-treatment at three and six months respectively for residual hematologic effects or other signs of AEs.

Of these patients, 145 underwent liver biopsy for disease staging prior to treatment initialization, as required for antiviral treatment approval at the time of the study.

Viral load was measured before treatment, after 12 doses and after eight months of treatment. Hemoglobin levels and thrombocyte counts were performed before the first antiviral dose, after 12 doses and after six months of treatment. Anemia was classified as mild for values between 10 g/dL and 11.5 g/dL for women and 13.7 g/dL for men, respectively and as moderate for values between 7 g/dL and 10 g/dL for both sexes. Baseline characteristics of the patients are presented in Table 2.

Table 1 – ***Gender, age and RBV dosage of patients. Age is expressed as means in years, with range in parentheses. Ribavirin dosage distribution in the patient group is expressed as numbers of patients, with percentages from the entire group in parentheses***

Feature	Men	Women
Gender	45	105
Age [years]	50 (28–64)	48 (25–64)
pegIFN + RBV 0.8 g	2 (1.3%)	17 (11.3%)
pegIFN + RBV 1 g	20 (13.3%)	71 (47.3%)
pegIFN + RBV 1.2 g	23 (15.3%)	17 (11.3%)

Table 2 – ***Baseline characteristics of patients. Results for hemoglobin, platelets, ALT and AST are expressed as medians, with range in parenthesis. Results for viral loads are expressed as means, with number of patients with detectable viremias in parentheses. Viral load was not calculated during the follow-up period***

Feature	Gender	Initial	Treatment			Follow-up	
		0	*12 doses*	*8 months*	*12 months*	*+3 months*	*+6 months*
Hemoglobin [g/dL]	*Men*	14.2 (10.9–16.9)	11.2 (9.1–14.7)	11.6 (9.6–16.3)	11.1 (9.8–16.1)	14.1 (11.1–16.4)	14.7 (10.8–16.9)
	Women	13.4 (10.6–15.6)	11.12 (8.2–12.1)	11.3 (7.8–11.9)	11 (7.9–12.2)	13.3 (10.2–15.3)	13.4 (10.7–15.8)
Platelets [$\times 10^4$/mm^3]	*Men*	19 (7.8–38.4)	15.4 (63.4–42.8)	16.6 (63.2–40.2)	16.7 (64.1–40)	18.8 (7.6–38.4)	19.1 (7.8–38.9)
	Women	20.4 (9.6–36.8)	16.65 (4.8–38.9)	16 (6.2–38.4)	16.2 (6.3–38.9)	20.1 (9.4–35.9)	20.4 (9.7–36.8)
ALT [U/L]	*Men*	88.3 (22–275)	30 (12–145)	26 (11.5–143)	27.3 (11.2–121)	28.1 (11–120)	29.3 (11.2–123)
	Women	99.5 (10–340)	28 (10–174)	34.5 (10–146)	30.2 (10–138)	29.4 (10–127)	29.6 (10–126)
AST [U/L]	*Men*	106 (26-324)	31 (14–172)	35.6 (11–123)	31.6 (12–120)	30.1 (11–119)	29.9 (11.1–118)
	Women	118.5 (9.2-382)	30 (9–274)	27 (11–181)	28.9 (10.1–126)	29.6 (11.2–158)	27.4 (10.9–182)
Viral load [IU/mL]	*Men*	878 000 (45)	2880 (7)	1120 (3)	1089 (2)	–	–
	Women	1 120 000 (105)	1127 (18)	1031 (4)	1012 (4)	–	–

Dermatologic and psychiatric consults were performed in each particular case as soon as the first symptoms were observed. Dermatologic assessment of cutaneous lesions was made by using the consecrated four-level grading scale and standard recommendations were followed regarding treatment management [1]. Patients were constantly monitored for constitutional adverse effects.

All patients signed informed consents prior to their inclusion, and the study received all necessary approval from the Ethics committees of the both University of Medicine and Pharmacy as well as the Emergency County Hospital of Craiova.

Statistical analysis of the results employed the use of the Kruskall–Wallis tests and Dunn multiple comparison test for assessing the variations in viral load, blood hemoglobin and platelet counts during treatment. Statistical significance required p-values <0.05.

Results

Minimum age was 25 for men and 28 for women, with a maximum of 64 years for both sexes (mean age 50±8.87 years for men, 48±9.15 years for women). We could observe a majority of cases between 40 and 60 years of age. All patients received pegIFN alpha-2a associated with different doses of RBV, as follows: 19 patients 0.8 grams, 91 patients 1 gram, while 40 patients received 1.2 grams of RBV (Table 1).

Liver histology

Liver biopsy was not possible in three men (one suffering from hemophilia, one undergoing anticoagulant treatment and one suffering from lymphoma, the later dying before the 12th antiviral dose) and two women, both having multiple liver hemagiomas. The majority of both sexes (24 men and 74 women) had an activity stage of A2; 11 men and 11 women were A1, 5 men and 18 women were A3 and only two men were A4. Fibrosis was staged as F3 in 26 men and 71 female, while 12 men and 32 women were F2 with only four men staged as F1. METAVIR score distribution showed a significant predominance of A2F3 for both sexes (18 men and 53 women; Figures 1–7).

Viral genotype, viral load and sustained virological response

All 150 patients were infected with the type 1 genotype HCV. Initial viral levels were between 100 000 and 1 million IU/mm^3 for 55.5% of the men (n=25) and 36.1% females (n=38), with 22.2% of men (n=10) and

29.5% of women (n=31) having between one and two million IU/mm^3 (Table 2). We could observe significant decrease in viral loads after 12 doses (Kruskall–Wallis test, p<0.001), with 15.9% men (n=7 out of 44 alive at that time) and 17.1% women (n=18) still having detectable viral activity. After eight months, 6.81% (n=3) men and 3.8% (n=4) women still had detectable viral loads. In the end, a total of six patients (4% of the studied group), two men and four women, respectively, were declared non-responders. There was no relationship between RBV doses, initial viral loads, and sustained virological response in our patient group (p=0.71).

Adverse effects

All patients experienced various degrees of anemia and thrombocytopenia during antiviral treatment. Mean initial hemoglobin levels were 14.2 g/dL for men and 13.4 g/dL for women; after eight months these values dropped significantly to 11.2 g/dL and 11.12 g/dL, respectively (Kruskall–Wallis test = 70.81 for men and 138.6 for women, p<0.0001 for both sexes). However, these values were not significantly different from those observed after 12 doses (11.6 g/dL for men and 11.3 g/dL for women, respectively; Dunn multiple comparison test p>0.05). Hemoglobin values remained low at the end of the 48 weeks of treatment, with no significant differences from the previous reported values (means of 11.1 g/dL for men and 11.0 g/dL for women, p>0.05). Of all patients, 78.6% (n=117 out of the remaining 149 patients) had mild anemia while the remaining 21.4% (n=32) had moderate anemia after 12 antiviral doses. After eight months of treatment, 39 patients showed moderate anemia, the rest having hemoglobin levels above 10 g/dL, corresponding to mild anemia. At three months of follow-up, 43 men and 101 women (97.3%) had normal levels of hemoglobin and all patients returned to normal values six months after treatment completion (Figure 8A).

Thrombocyte counts in men decreased after 12 doses (initial mean value 190 000/mm^3; 12-dose mean value 154 000/mm^3), going up to a mean of 166 000/mm^3 after eight months of antiviral treatment. We could observe a constant decrease in thrombocyte counts in women (from a mean value of 204 000/mm^3 to 166 500/mm^3 and 160 000/mm^3, respectively). Although values during antiviral therapy significantly decreased compared to pre-treatment figures (Kruskall–Wallis, p<0.05 for men; p<0.0001 for women), again we did not observe significant variation between 12-doses, eight-months and end of treatment values (Dunn multiple comparison test, p>0.05). During follow-up, 41 men and 99 women (93.9%) had normal platelet counts after three months, and all patients returned to normal values after six months since treatment completion (Figure 8B).

We found no significant relation between the severity of initial liver damage and the decrease of hemoglobin levels or thrombocytopenia (p=0.48). Also, RBV dosage did not influence the severity of the hematological adverse effects (p=0.89).

Overall, 43 patients (11 men and 32 women) had dermatological AEs (28.66% of the total group), such as rashes, drug eruptions and erythema. Mild rashes (grade 1) were present in 24% (n=36) of all cases, 9 men and 27 women, respectively, while the rest were classified as having grade 2 dermatological reactions (seven cases, 4.66% of the total group). Symptoms did not persist for more than a week and responded well to dermatological treatment, without requiring antiviral dose adjustments. We did not encounter any severe rashes or SCAR cases in our studied group. No other cutaneous side effects were reported during follow-up.

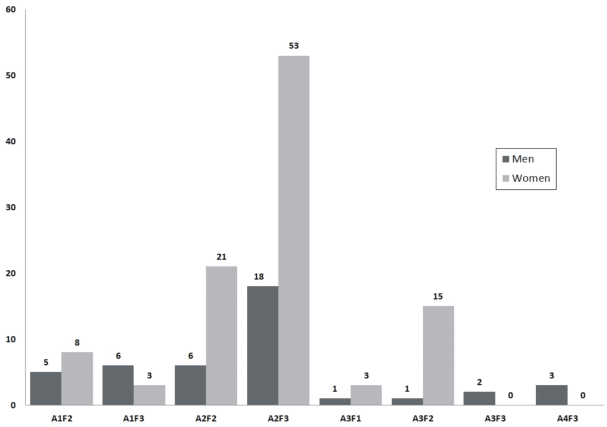

Figure 1 – ***Distribution of the METAVIR score in liver biopsies.***

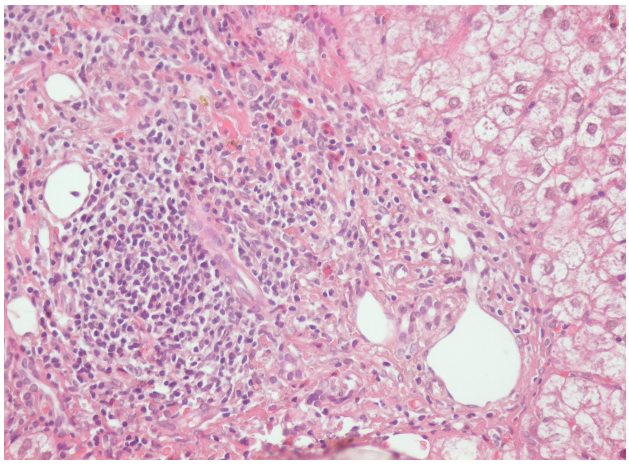

Figure 2 – ***Moderate inflammatory infiltrate of the portal space, with a regenerative nodule and portal fibrosis; hepatocytes with granulo-vacuolar degenerescence. Metavir Score: A2F1 (HE stain, ×200).***

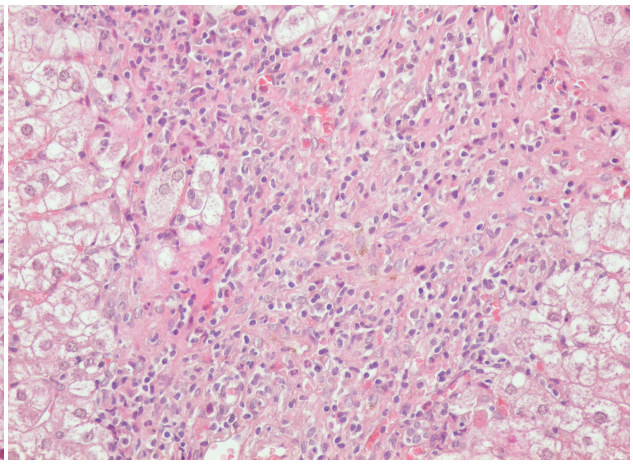

Figure 3 – ***Abundant inflammatory infiltrate of the portal space associated with interface hepatitis, fibrosis and hepatocytary apoptosis. Metavir Score: A2F3 (HE stain, ×200).***

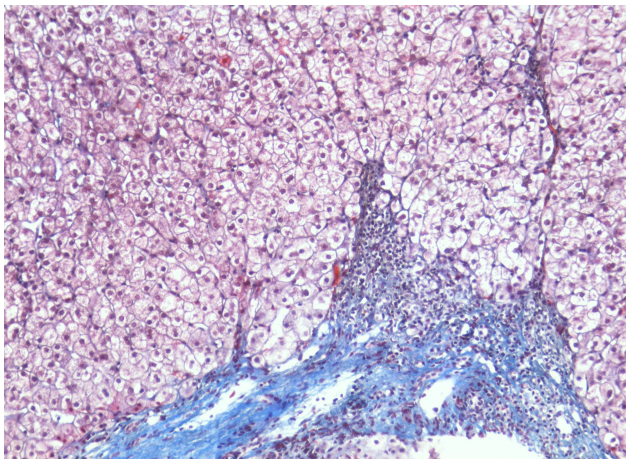

Figure 4 – ***Moderate inflammatory infiltrate associated with portal fibrosis and a tendency to form portal fibrous bridges. Granulo-vacuolar degenerescence of hepatocytes, more accentuated in the periportal space. Metavir Score: A2F2 (Trichromic Masson stain, ×100).***

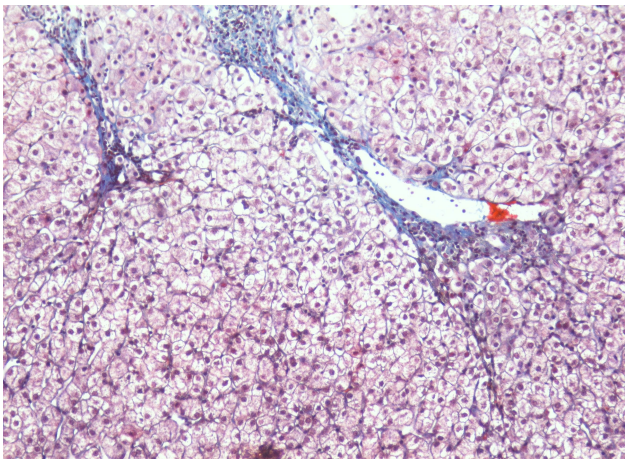

Figure 5 – ***Viral C hepatitis with granulo-vacuolar degenerescence, inflammatory infiltrate and fibrous bridges in the portal and portal-centrolobular spaces. Metavir Score: A1F3 (Trichromic Masson stain, ×100).***

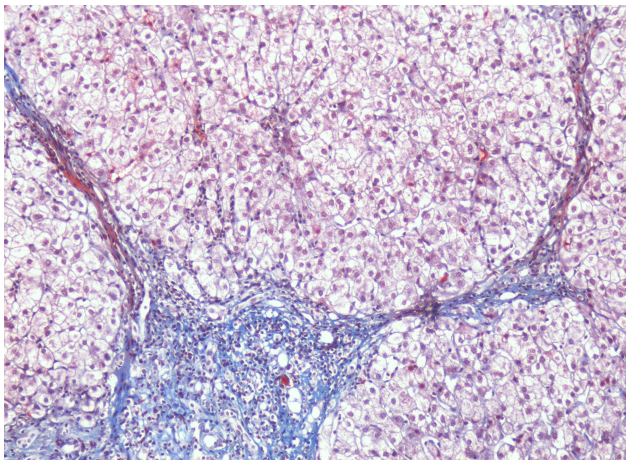

Figure 6 – ***Chronic C hepatitis with severe inflammation, portal fibrous bridges and intralobular fibrosis. Metavir Score: A3F3 (Trichromic Masson stain, ×100).***

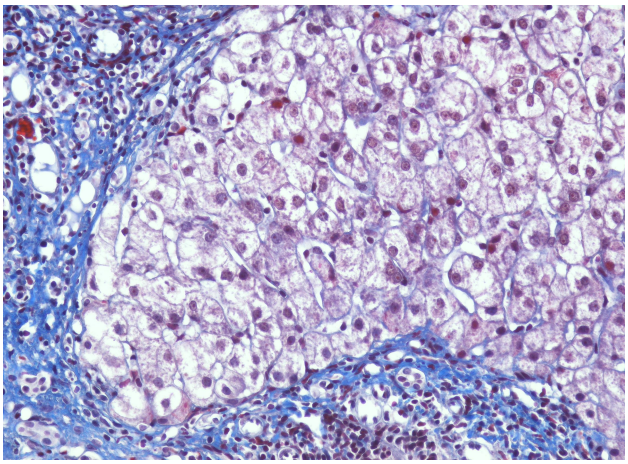

Figure 7 – ***Severe chronic C hepatitis with fibrosis and inflammation, hepatic apoptosis and cirrhotic pseudonodules. Metavir Score: A3F4 (Trichromic Masson stain, ×100).***

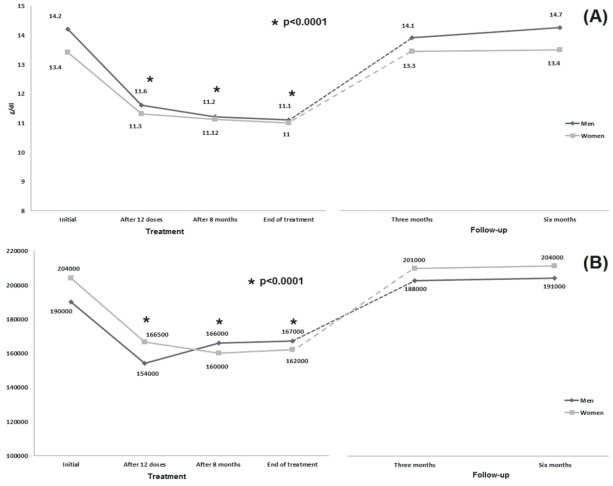

Figure 8 – ***Evolution of hematological parameters. We could observe a significant decrease in both hemoglobin values and platelet counts after 12 doses of treatment; however, the values did not decrease further during treatment, and returned to normal during the follow-up period. (A) Evolution of mean hemoglobin values; (B) Evolution of mean platelet counts.***

Psychiatric disorders were limited to mild cases of depression in 34 cases (10 men and 24 women, 22.6% of the group) which did not require specific medication or antiviral dose adjustment. Transient mood disorders were sporadically declared by the patients; however, they did not require psychiatric intervention. No suicidal tendencies or severe psychiatric disorders were reported. After treatment completion, no patient complained of further mood disorders.

Other adverse effects reported in the studied group were headaches (80.6% – 31 men and 90 women), fatigue (71.3% – 38 men and 69 women), nausea (47.3% – 18 men and 53 women), arthralgias (35.3% – 12 men and 41 women) and fever (30% of the total group – 14 men and 31 women). These symptoms were not reported during follow-up.

Discussion

We investigated the incidence of several AEs in a group of patients undergoing antiviral pegIFN alpha-2a/RBV treatment, while objectifying hematological changes during the course of treatment. We found that

initial disease state or RBV dosage had no effect on the severity of hematological AEs, while their severity did not increase during the course of the antiviral treatment.

In Romania, HCV-infected patients benefited from state-of-the-art pegIFNs and RBV treatments over the course of recent years, as therapy is fully reimbursed by the *National Health Insurance Agency* and pharmaceutical companies. Selection is based on rigorous criteria – severity of the disease, professional exposure, age, oncologic co-morbidities undergoing chemotherapy and time spent on the waiting list [18]. Until 2010, the severity of the disease was assessed through METAVIR determination, following liver biopsy wherever possible. This accounts for the large number of patients with METAVIR scores of A2F3 and above present in our study, as they were all successful candidates for antiviral therapy selection. The pre-imposed age criteria selected patients below 65 years.

Severe hematologic side effects are the primary cause of RBV dose reduction or even premature treatment interruption [19]. Anemia is mostly associated with RBV usage and sometimes requires dose reduction to reduce its effects. In our study, we could observe a decrease in hemoglobin levels throughout the entire group; however, no RBV dose-adjustment was necessary, as values remained constant during the course of treatment and we encountered no case of severe or life-threatening anemia. Decrease in platelets count is another frequent occurrence during combination antiviral therapy; however, it has been shown that their numbers rebound towards the end of the period [20]. Platelets count decreased after the first 12 doses of treatment in our study, and showed little to no decrease after eight months, even showing a mild increase in mean figures for men (from 154 000 at 12 doses to 166 000 after eight months). Hematological AEs will be amplified by the addition of novel DAAs to standard combined therapy, as shown by a number of recent studies [9, 21–24]. The high number of responders (143 patients, 96% out of the total 149 surviving patients, respectively, showed sustained virological response after 48 weeks of treatment, with 142 showing undetectable viral levels after eight months of treatment) is mainly due to the rigorous selection criteria imposed by the national authorities, which maximize treatment efficiency. The new combination therapies will mainly be available for relapsers and previous non-responders, therefore hematological effects will be foreseeable from existing data collected during previous combined pegIFN/RBV treatment.

Skin AEs were not severe, grades 1 or 2 being predominant in both men and women, and therefore did not require treatment interruption. We did not encounter any other severe AEs associated with cutaneous manifestations, and rashes were resolved after a few days of topic dermatologic treatment prescribed by the specialist. Recent studies [9, 14, 21–24] show an increase in rash and pruritus cases associated with triple antiviral therapy, compared to the pegIFN/RBV combination alone.

Besides the known influence of hepatitis viruses on the intrinsic stress mechanisms [25], antiviral therapies are known to cause mood disorders, which can sometimes lead to the need of psychiatric medication and even consecutive interruption of the antiviral treatment due to severe complications [15–17]. It is widely acknowledged that Interferon usage is responsible for these psychiatric AEs [17, 26], and therefore the use of DAAs will probably not influence the incidence or severity of these conditions. No patient included in our study required psychiatric treatment or required any alteration in the standard antiviral treatment regime.

The advent of new antiviral agents will open a new era of care for both previously untreatable HCV patients and for newly discovered cases [9, 21, 22]. However, the addition of DAAs will further enhance previously documented AEs, especially hematologic and dermatologic [10–14]. Triple antiviral therapy will become available in Romania in the coming years; therefore, it is necessary to assess the severity and prevalence of AEs during current antiviral protocols in order to predict future trends, as it was proven that better understanding of the incidence of AEs is important for maximizing the effect of the antiviral treatment [9, 21–27].

Conclusions

The severity and frequency of AEs is an important cause of abrupt antiviral treatment termination, leading to increased rates of unsuccessful therapies. Hematological AEs are present during pegIFN and RBV combination therapy, resulting in decreased levels of hemoglobin and platelet counts; however, their values return to normal after treatment completion. Cutaneous associated effects mainly include skin rashes and pruritus and are mostly limited to mild and moderate manifestations. We found no severe psychiatric side effect in our studied group, with a low incidence of depression that required psychiatric consult and further psychological counseling, without the need of any specific medication. In future, novel agents involved in antiviral therapies will lead to increased rates of sustained virological responses, at the cost of more pronounced associated AEs.

References

[1] Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M, *Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome*, Science, 1989, 244(4902):359–362.

[2] The Global Burden of Hepatitis C Working Group, *Global burden of disease (GBD) for hepatitis C*, J Clin Pharmacol, 2004, 44(1):20–29.

[3] Lavanchy D, *The global burden of hepatitis C*, Liver Int, 2009, 29(Suppl 1):74–81.

[4] ***, *Hepatitis C (Global alert and response, 2002)*, World Health Organization, Geneva, 2002, Updated: February 2010, http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/index.html.

[5] Zeuzem S, Yoshida EM, Benhamou Y, Pianko S, Bain VG, Shouval D, Flisiak R, Rehak V, Grigorescu M, Kaita K, Cronin PW, Pulkstenis E, Subramanian GM, McHutchison JG, *Albinterferon alfa-2b dosed every two or four weeks in interferon-naïve patients with genotype 1 chronic hepatitis C*, Hepatology, 2008, 48(2):407–417.

[6] Grigorescu M; Romanian Society of Gastroenterology and Hepatology, *HCV genotype 1 is almost exclusively present in Romanian patients with chronic hepatitis C*, J Gastrointestin Liver Dis, 2009, 18(1):45–50.
[7] 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, *Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection*, N Engl J Med, 2009, 361(6):580–593.
[8] Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H Jr, Bernstein D, Rizzetto M, Zeuzem S, Pockros PJ, Lin A, Ackrill AM; PEGASYS International Study Group, *Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose*, Ann Intern Med, 2004, 140(5):346–355.
[9] Kumada H, Toyota J, Okanoue T, Chayama K, Tsubouchi H, Hayashi N, *Telaprevir with peginterferon and ribavirin for treatment-naïve patients chronically infected with HCV of genotype 1 in Japan*, J Hepatol, 2012, 56(1):78–84.
[10] Hézode C, *Boceprevir and telaprevir for the treatment of chronic hepatitis C: safety management in clinical practice*, Liver Int, 2012, 32(Suppl s1):32–38.
[11] Bacon BR, Khalid O, *Triple therapy with boceprevir for HCV genotype 1 infection: phase III results in relapsers and non-responders*, Liver Int, 2012, 32(Suppl s1):51–53.
[12] Shiffman ML, Esteban R, *Triple therapy for HCV genotype 1 infection: telaprevir or boceprevir?* Liver Int, 2012, 32(Suppl s1):54–60.
[13] Lübbe J, Kerl K, Negro F, Saurat JH, *Clinical and immunological features of hepatitis C treatment-associated dermatitis in 36 prospective cases*, Br J Dermatol, 2005, 153(5):1088–1090.
[14] Cacoub P, Bourlière M, Lübbe J, Dupin N, Buggisch P, Dusheiko G, Hézode C, Picard O, Pujol R, Segaert S, Thio B, Roujeau JC, *Dermatological side effects of hepatitis C and its treatment: patient management in the era of direct-acting antivirals*, J Hepatol, 2012, 56(2):455–463.
[15] Jakiche A, Paredez EC, Tannan PK, Geppert C, Sontag VL, Qualls CR, Blair DA, Dettmer EL, *Trend of depression and the use of psychiatric medications in U.S. Veterans with hepatitis C during interferon-based therapy*, Am J Gastroenterol, 2007, 102(11):2426–2433.
[16] Lang JP, Melin P, Ouzan D, Rotily M, Fontanges T, Marcellin P, Chousterman M, Cacoub P; CheObs Study Group, *Pegylated interferon-alpha2b plus ribavirin therapy in patients with hepatitis C and psychiatric disorders: results of a cohort study*, Antivir Ther, 2010, 15(4):599–606.
[17] Zdilar D, Franco-Bronson K, Buchler N, Locala JA, Younossi ZM, *Hepatitis C, interferon alfa, and depression*, Hepatology, 2000, 31(6):1207–1211.
[18] Gheorghe L, Pascu O, Ceausu E, Csiki IE, Iacob S, Caruntu F, Simionov I, Vadan R, *Access to peginterferon plus ribavirin therapy for hepatitis C in Romania between 2002–2009*, J Gastrointestin Liver Dis, 2010, 19(2):161–167.
[19] Sung H, Chang M, Saab S, *Management of hepatitis C antiviral therapy adverse effects*, Curr Hepat Rep, 2011, 10(1):33–40.
[20] Fried MW, *Side effects of therapy of hepatitis C and their management*, Hepatology, 2002, 36(Suppl 1):S237–S244.
[21] Fried MW, The role of triple therapy in HCV genotype 1-experienced patients, Liver Int, 2011, 31(Suppl 1):58–61.
[22] Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, Poordad F, Goodman ZD, Sings HL, Boparai N, Burroughs M, Brass CA, Albrecht JK, Esteban R; HCV RESPOND-2 Investigators, *Boceprevir for previously treated chronic HCV genotype 1 infection*, N Engl J Med, 2011, 364(13):1207–1217.
[23] Dang SS, Wang WJ, Wang XF, Li YP, Li M, Jia XL, Wang Y, Liu E, Zhao S, *Telaprevir for chronic hepatitis C with genotype 1: a meta-analysis*, Hepatogastroenterology, 2012, 59(114):461–468.
[24] Corouge M, Pol S, *New treatments for chronic hepatitis C virus infection*, Med Mal Infect, 2011, 41(11):579–587.
[25] Vere CC, Streba CT, Streba LM, Ionescu AG, Sima F, *Psychosocial stress and liver disease status*, World J Gastroenterol, 2009, 15(24):2980–2986.
[26] Bonaccorso S, Marino V, Puzella A, Pasquini M, Biondi M, Artini M, Almerighi C, Verkerk R, Meltzer H, Maes M, *Increased depressive ratings in patients with hepatitis C receiving interferon-alpha-based immunotherapy are related to interferon-alpha-induced changes in the serotonergic system*, J Clin Psychopharmacol, 2002, 22(1):86–90.
[27] Vere CC, Neagoe D, Streba CT, Prejbeanu I, Ianoşi G, Comănescu V, Pirici D, *Steatosis and serum lipid patterns in patients with chronic viral hepatitis: differences related to viral etiology*, Rom J Morphol Embryol, 2010, 51(3):509–514.

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Received: March 6th, 2012

Accepted: August 25th, 2012