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.
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.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>50 (28–64)</td>
<td>48 (25–64)</td>
</tr>
<tr>
<td>pegIFN + RBV 0.8 g</td>
<td>2 (1.3%)</td>
<td>17 (11.3%)</td>
</tr>
<tr>
<td>pegIFN + RBV 1 g</td>
<td>20 (13.3%)</td>
<td>71 (47.3%)</td>
</tr>
<tr>
<td>pegIFN + RBV 1.2 g</td>
<td>23 (15.3%)</td>
<td>17 (11.3%)</td>
</tr>
</tbody>
</table>

Table 2 – Baseline characteristics of patients. Results for hemoglobin, platelets, ALT and AST are expressed as medians, with range in parentheses. 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.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Initial</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin [g/dL]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>14.2 (10.9–16.9)</td>
<td>11.2 (9.1–14.7)</td>
<td>14.1 (11.1–16.4)</td>
</tr>
<tr>
<td>Women</td>
<td>13.4 (10.6–15.6)</td>
<td>11.12 (8.2–12.1)</td>
<td>13.3 (10.2–15.3)</td>
</tr>
<tr>
<td>Platelets [×10^12/mm^3]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>19 (7.8–38.4)</td>
<td>15.4 (63.4–42.8)</td>
<td>18.8 (7.6–38.4)</td>
</tr>
<tr>
<td>Women</td>
<td>20.4 (9.6–36.8)</td>
<td>16.65 (4.8–38.9)</td>
<td>20.1 (9.4–35.9)</td>
</tr>
<tr>
<td>ALT [IU/L]</td>
<td>88.3 (22–275)</td>
<td>30 (12–145)</td>
<td>28.1 (11–120)</td>
</tr>
<tr>
<td>Women</td>
<td>106 (26–324)</td>
<td>31 (14–172)</td>
<td>30.1 (11–119)</td>
</tr>
<tr>
<td>AST [IU/L]</td>
<td>118.5 (9.2–382)</td>
<td>30 (9–274)</td>
<td>29.6 (11.2–158)</td>
</tr>
<tr>
<td>Men</td>
<td>878 000 (45)</td>
<td>2880 (7)</td>
<td>28.9 (10.1–126)</td>
</tr>
<tr>
<td>Women</td>
<td>1 120 000 (105)</td>
<td>1127 (18)</td>
<td>27.4 (10.9–182)</td>
</tr>
</tbody>
</table>

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 latter 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 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.
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](image1.png)

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

![Figure 2](image2.png)

**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](image3.png)

**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).

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 relapers 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 topical 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

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