

## The follow-up of the efficacy of antiviral therapy at patients with chronic hepatitis C

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### Abstract

Hepatitis C virus infection can cause progressive liver injury and lead to fibrosis and eventually cirrhosis. Peginterferon alfa-2a represents a significant advance in the treatment of patients with chronic hepatitis C. The aim of the study was to investigate the efficacy, safety and tolerability of the therapy with Peginterferon alfa-2a plus Ribavirin in patients with chronic hepatitis C. The study was made on a number of 37 patients with chronic hepatitis C, admitted in Medical Clinic no. 1, Emergency County Hospital Craiova. The diagnosis of chronic hepatitis was established by means of clinical, biological and morphological investigations. Patients received 180 µg subcutaneously of Pegasys, once weekly, along with either 1000 or 1200 mg/day of Copegus, depending on their weight, for 48 weeks, with 24 weeks of treatment – free follow-up. We evaluated: sustained virological response, histological response and adverse events. All patients were monitored using blood tests, control of viremia and liver functional tests. Analysis viral response revealed that 11 patients (29.72%) achieved sustained virological response. Histological response was obtained in 20 cases (54.05%) with chronic hepatitis C. The adverse events for Pegasys and Copegus combination therapy were reported in 21 cases (56.72%). Antiviral therapy had positive effect on subjective symptoms in almost half of patients included in our study. An improvement of liver functional tests was noted in the most cases. A third of patients who received Peginterferon alfa-2a plus Ribavirin had sustained virological response. Histological response was noted both at patients with sustained virological response and with unsustained virological response. The side effects of the antiviral treatment are frequent and the severe ones, which require dose reduction, are present at a low number of patients.

**Keywords:** Peginterferon alfa-2a, Ribavirin, chronic hepatitis C.

### Introduction

Chronic hepatitis C is a public health major problem by unfavorable spontaneous evolution and numerous complications due to this disease.

Hepatitis C virus (HCV) infection can cause progressive liver injury and lead to fibrosis and eventually cirrhosis.

Peginterferon alfa-2a represents a significant advance in the treatment of patients with chronic hepatitis C.

The pharmacokinetic and pharmacodynamic profiles of Pegasys are reflected in significant improvements in virological response to treatment [1].

The aim of the study was to investigate the efficacy, safety and tolerability of the therapy with Peginterferon alfa-2a plus Ribavirin in patients with chronic hepatitis C.

### Material and methods

The study was made on a number of 37 patients with chronic hepatitis C, 10 males (27.02%) and 27 females (72.98%), with average age  $50.21 \pm 10.72$ , years admitted in Medical Clinic no. 1, Emergency County Hospital Craiova.

The diagnosis of chronic hepatitis was established by means of clinical, biological and morphological investigations.

All patients were interferon-naïve with anti-HCV

antibodies, quantifiable HCV RNA by polymerase chain reaction (PCR), normal or elevated aminotransferase (ALT  $>1.5 \times N$ ) levels and compensated liver disease.

In all the cases we have performed liver biopsies and histopathological exam before starting antiviral therapy and reviewed after 48 weeks of treatment.

The biopsies were evaluated by local pathologist using the Knodell histology activity index – Knodell's score of necroinflammatory activity = 6 and fibrosis  $<3$  (Table 1).

The necroinflammatory and fibrosis scores are added together to give a total HAI (Histological Activity Index) score.

All patients had middle or severe histological changes of chronic hepatitis before starting antiviral therapy [2].

Patients received 180 µg subcutaneously of Pegasys, once weekly, along with either 1000 or 1200 mg/day of Copegus, depending on their weight, for 48 weeks, with 24 weeks of treatment, free follow-up [3–7].

We evaluated: sustained virological response, histological response and adverse events.

Sustained virological response was definite as undetectable HCV RNA at the end of follow-up (week 72).

Histological response was definite as a  $\geq 2$  points reduction from baseline in the total HAI score.

All patients were monitored using blood tests, control of viremia and liver functional tests.

Table 1 – Knodell Score

| HISTOLOGY ACTIVITY INDEX (HAI – KNODELL SCORE)   |       |  |       |   |       |   |       |
|--|-------|--|-------|---|-------|---|-------|
| Periportal ± Bridging necrosis   | Score | Intralobular degeneration and focal necrosis   | Score | Portal inflammation   | Score | Fibrosis  | Score |
| None   | 0     | None   | 0     | No portal inflammation  | 0     | No fibrosis   | 0     |
| Mild piecemeal necrosis  | 1     | Mild (acidophilic bodies, ballooning degeneration and/or scattered foci of hepatocellular necrosis in 1/3 of lobules or nodules)   | 1     | Mild (sprinkling of inflammatory cells in <1/3 of portal tracts)      | 1     | Fibrous portal expansion                                    | 1     |
| Moderate piecemeal necrosis (involves <50% of the circumference of most portal tracts) | 3     | Moderate (involvement of 1/3–2/3 of lobules or nodules)  | 3     | Moderate (increased inflammatory cells in 1/3–2/3 of portal tracts)   | 3     | Bridging fibrosis (portal–portal or portal–central linkage) | 3     |
| Marked piecemeal necrosis (involves >50% of the circumference of most portal tracts)   | 4     | Marked (involvement of >2/3 of lobules or nodules)   | 4     | Marked (dense packing of inflammatory cells in >2/3 of portal tracts) | 4     | Cirrhosis   | 4     |
| Moderate piecemeal necrosis <i>plus</i> bridging necrosis                              | 5     | <u>Reference</u>   |       |   |       |   |       |
| Marked piecemeal necrosis <i>plus</i> bridging necrosis                                | 6     | KNODELL R. G., ISHAK K. G., BLACK W. C. <i>et al.</i> , <i>Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis</i> , <i>Hepatology</i> , 1981, 1:431–435. |       |   |       |   |       |
| Multilobular necrosis  | 10    |  |       |   |       |   |       |
| <b>Total HAI (Knodell Score) = ___/22</b>  |       |  |       |   |       |   |       |

## ☐ Results

The antiviral therapy had positive effect on subjective symptoms (right upper quadrant pain, asthenia, postprandial meteorism, nausea, dyspeptic syndrome) in 16 cases (43.24%). The baseline viral load was more than 100 000 copies/ml. Viremia became undetectable after three months of therapy with Pegasys and Copegus in all patients, thus we continued the study according to the protocol.

The alanine aminotransferase (ALT) levels were  $56 \pm 11.95$  UI/ml before starting treatment. We observed a low increase of ALT within the first two months of therapy, than decreased to  $21.45 \pm 13.07$  UI/ml after 48 months of antiviral therapy.

We evaluated others biochemical parameters too. Thus, bilirubin levels increased within the first months of treatment, then decreased after three months of therapy to 1.07 mg/dl gamma-glutamyl-transpeptidase levels decreased from 47 UI/ml to 43.91 UI/ml after finishing the therapy, and alkaline phosphatase levels decreased from 236.99 UI/l to 227.82 UI/l.

Analysis viral response revealed that 11 patients (29.72%) achieved sustained virological response.

From the histological point of view (Hematoxylin-Eosin and Gömöri staining), middle hepatitis was found in 24 cases (64.86%) and severe hepatitis in 13 cases (35.14%) (Figures 1–4).

Regarding fibrosis, score  $\leq 3$  for fibrosis was found in 19 patients (51.35%) and score 1 for fibrosis in 18 patients (48.65%).

Histological response was obtained in 20 cases (54.05%) with chronic hepatitis C. We noted that all patients with sustained virological response had histological response and nine patients (24.32%) with unsustained virological response showed an improvement in hepatic histological changes.

Table 2 – Histological response in patients with virological response treated with Peginterferon plus Ribavirin

| Histological response            | No. of patients |
|----------------------------------|-----------------|
| Sustained virological response   | 11              |
| Unsustained virological response | 9               |
| <b>Total</b>                     | <b>20</b>       |

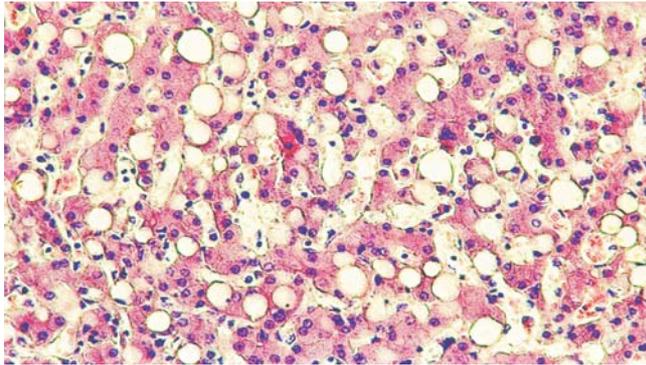
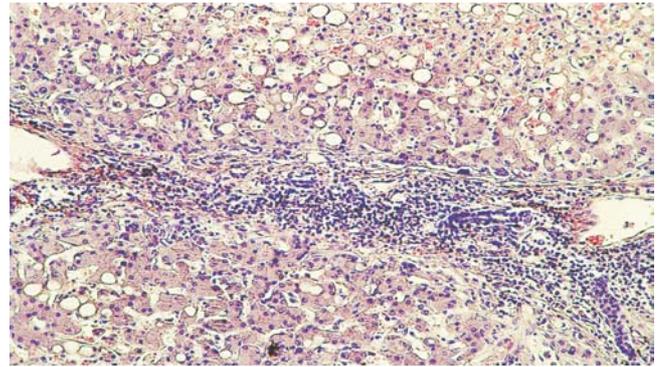
The adverse events for Pegasys and Copegus combination therapy were reported in 21 cases (56.72%): hematologic abnormalities – seven cases (18.91%), fatigue – five cases (13.5%), headache – four cases (10.54%), myalgia – two cases (5.4%), depression – two cases (5.4%), and alopecia – one case (2.7%).

The hematological abnormalities were: anemia – one case (2.7%), neutropenia – five cases (13.5%), and thrombocytopenia – one case (2.7%). During therapy, hemoglobin levels decreased within the first 24 weeks of therapy with a mean maximal decrease of approximately 3 g/dl, but only in one case (2.7%) was necessary dose reduction. Hematological abnormalities required dose reduction. Evolution was favorable in all those patients after dose reduction (Figure 5).

## ☐ Discussions

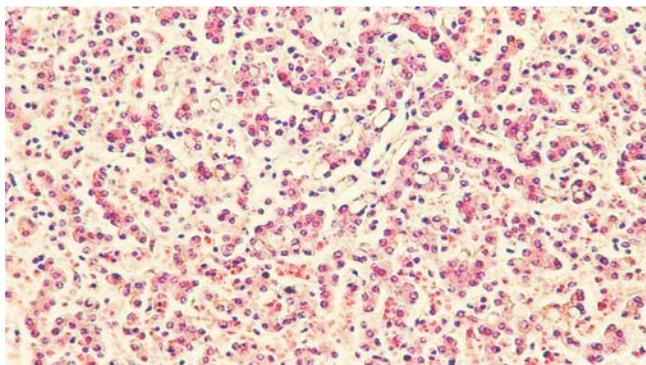
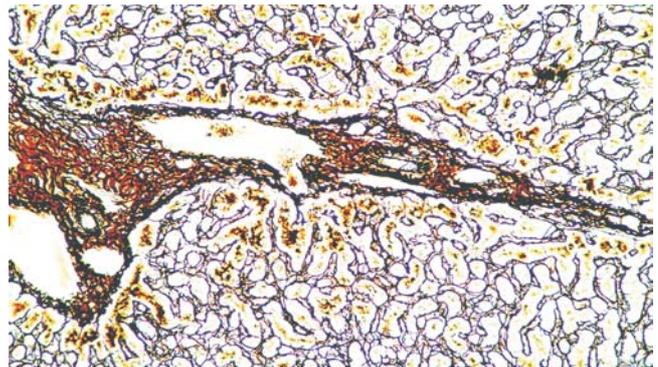
The treatment with Peginterferon alfa-2a plus Ribavirin had positive effect on subjective symptoms in nearly half of patients included in our study. During therapy we registered hematological abnormalities, such anemia, neutropenia and thrombocytopenia, in some cases. Hemoglobin levels decreased within the first 24 weeks of therapy with a mean maximal decrease of approximately 3 g/dl, but only in 1 case (2.7%) was necessary dose reduction. Neutropenia and thrombocytopenia were observed in six cases (16.21%) and require dose reduction. Regarding the evolution of biochemical parameters we observed a low increase of aminotransferase levels within the first two months, and then ALT normalized during antiviral therapy.

**Figure 1 – Middle hepatitis. Moderate piecemeal necrosis and mild inflammatory cells of portal tracts (HE staining, ×100)**



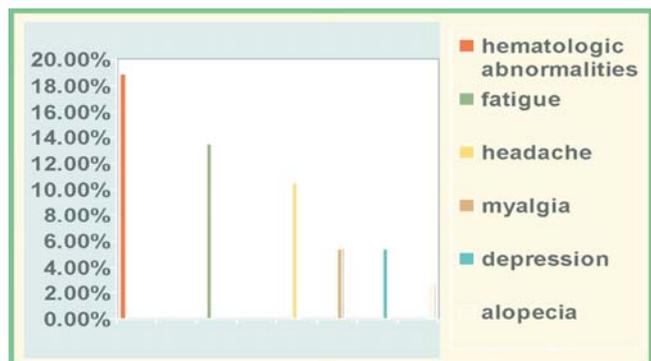
**Figure 2 – Middle hepatitis associated with steatosis (HE staining, ×200)**

**Figure 3 – Middle hepatitis associated with interlobular fibrosis (Gömöri's argentic impregnation, ×100)**



**Figure 4 – Severe hepatitis. Marked piecemeal necrosis and marked inflammatory cells of portal tracts (HE staining, ×100)**

**Figure 5 – Adverse events in antiviral treatment at patients with chronic hepatitis C**



In the same time, we registered also a decrease of the viral load, which was undetectable after three months of treatment, according to a virological response after 48 weeks of therapy [4, 8].

In the most cases we noted a tendency to normalize of the liver functional tests, according to the histological improvement registered after cessation of therapy [4, 9, 10–12].

Biopsies were done to all patients after finishing treatment. Histopathological exam showed a decrease of Knodell score with more than three points comparatively with baseline. Despite recent advances in biochemical, serologic and radiological techniques, liver biopsies remain an essential component of diagnostic and management decisions in patients with chronic viral hepatitis. Liver biopsy provides information about the extent and distribution of inflammation and allows grading and staging of the disease [13–17].

Although antiviral therapy is the only choice who's giving the real results, still, many patients do not have a good response or they relapse after breaking off the treatment [18].

A third of patients with HCV infection treated with Peginterferon alfa-2a plus Ribavirin had a sustained virological response. In all these cases the sustained virological response was accompanied by histological improvement. Importantly, histological improvement after antiviral therapy was observed in patients with unsustained virological response [19, 20].

Incidence rates for adverse events were generally higher among patients with chronic hepatitis C who received Pegasys and Copegus. The most common side effects were hematological abnormalities follow by fatigue, headache, myalgia, neuropsychiatric symptoms and alopecia. The secondary effects are more important to the oldest patients and to women. The important adverse events witch imposed to reduce the doses are few and the evolution during therapy of these patients was favorable [5, 10].

## ✉ Conclusions

Antiviral therapy had positive effect on subjective symptoms in almost half of patients included in our study. An improvement of liver functional tests was noted in the most cases. A third of patients who received Peginterferon alfa-2a plus Ribavirin had sustained virological response. Histological response was noted both at responders and non-responders patients with chronic hepatitis C.

The side effects of the antiviral treatment are frequent and the severe ones, which require dose reduction, are present at a low number of patients.

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