Antiviral therapy effects upon hepatitis C cholestatic syndrome

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Abstract
Cholestasis includes, as a syndrome, all clinical and biological manifestations caused by the deficient or simply absent biliar secretion or caused by the obstruction of the biliary ducts. The hepatic cholestasis from the chronic hepatitis C (HC VHC) is a result of the altered interlobular biliary canalicules, caused by the modified cellular transport mechanisms and it is associated with a medium to severe degree of fibrosis. The aim of this study was to evaluate the efficiency of antiviral therapy in HC VHC patients. The study included a number of 37 HC VHC patients admitted at the Medical Department no. 1 of the Emergency County Hospital of Craiova; they were treated with Pegasys, 180 µg/week and Copegus, 1000 or 1200 mg/day, taking in consideration their weight, for 48 weeks and they were monitored for 24 weeks after the treatment. The following parameters were analyzed: direct bilirubine, total cholesterol, alkaline phosphatase, gamma-glutamiltranspeptidase and leucin-aminopeptidase. Under treatment, the clinical status caused by the cholestasis (pruritus, icteric syndrome, hemorrhagic syndrome) was improved in six of the given cases (16.22%). Before therapy, the hepatic cholestasis was present in 20 patients (54.05%), and after treatment in 14 patients (37.83%). During therapy, the average values for all the monitored parameters decreased: direct bilirubine (0.38 ± 0.18 mg/dl vs. 0.34 ± 0.24 mg/dl, p = 0.0867), total cholesterol (198.53 m/dl vs. 183.16 m/dl, p = 0.0808), alkaline phosphatase (236.99 ± 79.09 iu/l vs. 227.82 ± 87.59 iu/l, p = 0.0845), gamma-glutamiltranspeptidase (47 ± 32.89 iu/l vs. 43.91 ± 29.66 iu/l, p = 0.1509), and leucin-aminopeptidase (32.33 ± 13.22 iu/l vs. 28.95 ± 14.22 iu/l, p = 0.0038). Under antiviral treatment there was noticed an improvement of the cholestasis clinical status in a small number of cases. Antiviral therapy favorably influenced the liver cholestasis associated in patients with chronic hepatitis C in a rather small proportion. Under Interferon pegylate and Ribavirine treatment, low levels of direct bilirubine, cholesterol and enzymes were found. Hepatic cholestasis and, especially, the high serum values of gamma-glutamiltranspeptidase have a negative influence upon antiviral therapy, causing the low sustained virological response.

Keywords: type C viral hepatitis, cholestasis, antiviral therapy.

Introduction
Cholestasis includes the totality of both clinical and biological manifestations determined by the reduction or absence of the biliary secretion or by the biliary ducts obstruction. Hepatic cholestasis in chronic hepatitis C is caused by the alteration of the interlobular bile ducts and possibly by the modified intercellular transport mechanisms and it is associated with a medium to high fibrosis level [1].

The purpose of the study was to measure the efficiency of the antiviral treatment used in HC VHC patients suffering with the cholestatic syndrome.

Material and methods
The research included a number of 37 patients with HC VHC, from the Medical Department no. 1 of the Emergency County Hospital of Craiova; they were treated with Pegasys, 180 µg/week and Copegus, 1000 or 1200 mg/day, taking in consideration their weight, and they were monitored for 24 weeks after the treatment [2–9].

The diagnosis of chronic hepatitis was established using clinical, biological and morphological criteria. Both the sustained virological and histological responses were under observation [10–15].

All patients were investigated periodically through hemograms, viral level s and functional liver tests.

The following biochemical parameters were studied attentively: direct bilirubine, total cholesterol, alkaline phosphatase, gamma-glutamiltranspeptidase and leucin-aminopeptidase.

Results
Before initiating the antiviral therapy, the clinical manifestations of cholestasis were observed in 16 cases (43.24%): 12 cases with pruritus and icter, two cases (5.4%) with steatoreea, and two cases (5.4%) with rashes.

Under antiviral treatment, there was noticed an improvement in six clinically active cholestasis cases (16.22%): four cases (10.81%) with pruritus and icter, one case (2.7%) with steatoreea and one case (2.7%) with rashes.
Hepatic cholestasis was present in 20 cases (54.05%) before treatment and by the end of therapy only 14 cases (37.83%) were left. Icteric cholestasis was initially seen in 12 cases (32.43%), and after the treatment in only eight cases (21.62%); while non-icterical cholestasis was observed before therapy in eight cases (21.62%), and by the end of the research there was noticed in six cases (16.21%).

During therapy, all the average values of the cholestatic parameters were estimated at lower levels (Table 1). Thus, the plasma value for direct bilirubine was 0.38 ± 0.28 mg/dl before treatment with high levels in 12 cases (32.43%) and after treatment it was 0.34 ± 0.24 mg/dl (p = 0.0867), maintaining a high rate in eight cases (21.62%).

The plasmatic level for the total cholesterol was found to be normal in all cases during the initial phase of the study, with a value of 198.53 mg/dl, and it decreased by the end of the research at a rate of 183.16 mg/dl (p = 0.0808).

The serum level of the alkaline phosphatase was at first high in eight cases (21.62%) and it slightly reduced from 236.99 ± 79.09 iu/l to 227.82 ± 87.59 iu/l (p = 0.0845), by the end of the program maintaining high values in six cases (16.21%).

Gamma-glutamiltranspeptidase had at the beginning a high concentration in 20 cases (54.05%) and it dropped easily to 43.91 ± 29.66 iu/l (p = 0.1509), having the same high levels in 14 cases (37.83%).

The serum level of leucin-aminopeptidase was 32.33 ± 13.22 iu/l, before therapy, being high in 14 cases (37.83%) and after the therapy it reached a low level of 28.95 ± 14.22 iu/l (p = 0.0038), with high serum concentrations in nine cases (24.32%).

Table 1 – The evolution of the biochemical parameters in cholestasis under antiviral therapy

<table>
<thead>
<tr>
<th>Biochemical parameters</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct bilirubine</td>
<td>0.38 ± 0.28 mg/dl</td>
<td>0.34 ± 0.24 mg/dl</td>
<td>0.0867</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>198.53 mg/dl</td>
<td>183.16 mg/dl</td>
<td>0.0808</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>236.99 ± 79.09 u/l</td>
<td>227.82 ± 87.59 u/l</td>
<td>0.0845</td>
</tr>
<tr>
<td>Gamma-glutamil</td>
<td>47 ± 32.89 u/l</td>
<td>43.91 ± 29.66 u/l</td>
<td>0.1509</td>
</tr>
<tr>
<td>transpeptidase</td>
<td>32.33 ± 13.22 u/l</td>
<td>28.95 ± 14.22 u/l</td>
<td>0.0038</td>
</tr>
</tbody>
</table>

Discussion

Hepatic cholestasis was evidenced in approximately half the chronic hepatitis C cases included in the study. A moderate follows up cholestasis associated with the hepatitis virus C infection to severe level of fibrosis and it is caused by the alteration of the interlobular bile ducts – which is partially due to a ductal proliferation and partially due to a slight duct malfunction. Another incriminated factor causing the hepatic cholestasis in chronic hepatitis C patients might be the damaged cellular transport mechanisms [15, 16].

For the histological evaluation, the Knodell score was used (necro-inflammatory activity = 6, and fibrosis= 3). Histological analyses were made in every given case by the end of the therapy, hepatic biopsy showing a 3-point decrease of the Knodell score in comparison to the initial values (Figures 2–4) [17].

The histological improvement under Peginterferon alfa-2a and Ribavirine was accompanied by a clinical remission in a small number of cases. From all clinical aspects, a larger improvement was observed in pruritis and icter. Pruritis was present in one third of the cases in the initial stage of treatment, especially in patients with high levels of transaminases, alkaline phosphatase and gamma-glutamiltranspeptidase, and in patients with fibrosis. A small number of patients were clinically prurit-free by the final stages of the research and this result was associated with the improvement of the functional liver tests and the hepatic histological modifications under antiviral drug administration [18].

Paraclinical lab tests showed all biochemical studied parameters for cholestasis to be lower in addition to the improvement of the histological modifications. Out of the cholestasis enzymes, gamma-glutamiltranspeptidase has registered high levels in most of the cases. Patients with high gamma-glutamiltranspeptidase rates have generally suffered from a severe liver fibrosis and a low sustained virusological response.

The antiviral therapy response was obtained for an approximately one third of the patients, a lower result than most other reports mentioned in published medical works. This fact can be explained partially by the presence of the cholestasis and, especially by high gamma-glutamiltranspeptidase serum levels in a significant number of cases.

Cholestasis and biliary acids inhibit the protein induction implicated in the antiviral interferon activity, such as oligoadenilate, while the mechanism through which gamma-glutamiltranspeptidase causes the deficient sustained virusological response at the antiviral therapy remains unknown [19, 20].

Conclusions

Under antiviral treatment, an improvement of clinical manifestation in a low number of cases was observed.

Antiviral therapy favorably influenced intrahepatic cholestasis associated with chronic hepatitis C in a relatively small number of patients.

Under Interferon pegylate and Ribavirine treatment, the serum levels of direct bilirubine, cholesterol and cholestasis enzymes were decreased.

Intrahepatic cholestasis and, especially, the high serum levels of gamma-glutamil transpeptidase have a negative influence over antiviral therapy, causing the low rate of sustained virusological response.

References


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Figure 1 – The evolution of the clinical manifestations in cholestasis under antiviral therapy

Figure 2 – Chronic hepatitis C: necrosis and inflammation; moderate steatosis

Figure 3 – Chronic hepatitis C: extensive fibrosis

Figure 4 – Chronic hepatitis C: fibrosis and abundant lymphoplasmocytary infiltrate in the Kiernann space


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