Combined interferon-alpha-2b and ribavirin therapy in patients with recurring chronic hepatitis C (genotype 1) following liver transplantation in Hungary

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Abstract

Objectives: Hepatitis C virus (HCV) recurrence after liver transplantation is universal and leads to chronic hepatitis and cirrhosis. Combined interferon and ribavirin therapy represents the accepted treatment for recurrent chronic hepatitis C following liver transplantation, according to the literature. Our aim was to assess the efficacy and safety of the recommended combined interferon and ribavirin therapy, and evaluation of the rate of long-term remission under Hungarian circumstances.

Methods: 16 patients with chronic recurrent hepatitis C, who had been HCV-PCR positive (genotype 1b), received combined treatment with interferon-alpha-2b (3 MU three times a week) and ribavirin (800-1000 mg daily) for 12 months following transplantation. 12 patients have completed the therapy. Liver biopsies were performed before commencing and after concluding treatment in every patient. Virological responses at completion of the 12-month-long treatment and at the end of the subsequent 6-month-long follow-up period served as endpoints for the evaluation.

Results: At completion of the 12-month-long treatment 3 patients became HCV-PCR-negative. All three patients remained negative at six months following completion of the treatment.

Conclusions: Efficacy and safety of the combined treatment of transplanted patients were similar to the therapeutic results in patients with chronic hepatitis C without liver transplantation.

Key words: chronic hepatitis C, interferon, ribavirin, liver transplantation.

Introduction

There is no sure therapeutic method for the elimination of hepatitis C virus (HCV) from the human organism. In chronic hepatitis C, elimination of the virus can be attained with long-term interferon treatment in about 10-20% [1, 2, 3], with combined interferon and ribavirin treatment in 20-40% [1, 4-7], and with pegylated interferon and ribavirin therapy in 40-60% [8, 9] of the cases. The therapy is more effective in viral genotypes 2 and 3, while it confers less benefit on genotypes 1 and 4. If elimination of the virus is not
possible, end-stage hepatic cirrhosis develops in patients with chronic hepatitis C. In this case, an improvement of the patient’s state can only be assured by liver transplantation.

After transplantation, however, HCV infection usually returns almost in every case, if the patient could not be made virus-free previously [10]. Antiviral therapy is recommended in patients on the waiting list, even with uncompensated cirrhosis [11]. In transplanted patients, de novo HCV infection is very rare due to the regular screening for HCV [12]. The course of recurrent hepatitis C infection is shown in figure 1. The severity of the disease is influenced by several factors [10]. These may be related to viral characteristics (number of viruses, viral genotype), may depend on the donor (age, sex, sexual relations), may be consequences of the surgical intervention (warming, duration of ischemia), or properties of the recipient (HLA, state of the immune system), as well as changes developing because of external factors (immunosuppressive treatment, alcohol, concomitant viral infection, years passed after transplantation, and antiviral therapy).

In this report we have collected our experiences obtained during the treatment at the 2nd Department of Medicine of patients with chronic recurrent hepatitis C, who underwent liver transplantation at the Department of Transplantation Surgery of the Semmelweis University, Budapest.

Materials and methods

16 patients of both sexes (10 male and 6 female), aged between 36 and 63 years (mean age: 45.1 years), and suffering from chronic hepatitis C have been enrolled. The diagnosis was established by the clinical symptoms, on the base of the serum alanin-aminotransferase (ALT) activity, the molecular markers of HCV infection (anti-HCV-positive state, HCV-RNA test), as well as the histological examination of the liver (Knodell-index). All patients carried the genotype 1b of HCV.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>8/4</td>
</tr>
<tr>
<td>Mean age</td>
<td>45.1 (36-63) years</td>
</tr>
<tr>
<td>Number of rejections before treatment</td>
<td>3</td>
</tr>
<tr>
<td>Genotype 1b</td>
<td>12</td>
</tr>
<tr>
<td>Mean ALT</td>
<td>159.1 U/L</td>
</tr>
<tr>
<td>Mean bilirubin</td>
<td>32.0 µmol/L</td>
</tr>
<tr>
<td>Mean HCV-RNA</td>
<td>450 copies/mL (145-1800)</td>
</tr>
<tr>
<td>Mean staging score</td>
<td>1.91</td>
</tr>
<tr>
<td>Mean grading score</td>
<td>8.27</td>
</tr>
<tr>
<td>Mean hemoglobin</td>
<td>140 g/L</td>
</tr>
<tr>
<td>Mean platelet count</td>
<td>1.6x10⁹/L</td>
</tr>
<tr>
<td>Mean leucocyte count</td>
<td>4.925 x10⁹/L</td>
</tr>
<tr>
<td>Average time lag after liver transplantation before the start of the treatment</td>
<td>14.3 (3-36) months</td>
</tr>
</tbody>
</table>

Table I. Baseline values of patients receiving combined therapy

End stage liver disease caused by HCV infection is the indication of liver transplantation in 35-50% of the cases

Liver transplantation

Recurrent infection is more than 98%

Follow-up for 1-13 months

Acute hepatitis: 25-45%

Follow-up for 5 years

Factors related to the virus

- HCV induced chronic hepatitis: 80-100%
- Graft cirrhosis related to HCV: 80-30%
- Cholestatic hepatitis: 2-8%

Factors related to the host

Donor characteristics

Surgical factors

External factors

Figure 1. Natural course of hepatitis C following liver transplantation
Baseline data of the treated patients are shown in Table I.

According to the protocol of the clinical treatment, the interferon-alpha-2b product (Intron A, Schering-Plough, Co.) was administered three times a week, in a dose of 3.0 MU, in subcutaneous injections; and ribavirin (Rebetol, Schering-Plough, Co.) was given orally in a daily dose of 800-1000 mg, depending on the body mass. Duration of the treatment was one year, and the follow-up period lasted for further 6 months. Four patients were withdrawn from the study due to adverse effects, mainly for severe anemia. Reduction in the dose of ribavirin in 3 of 12 cases was due to the onset of anemia.

Clinical and laboratory examinations of the patients were performed at 1, 2, 4, 6, and 8 weeks after enrollment into the program, then in every month. Follow-up observations were performed after completion of the treatment, at three months’ intervals. Data of the treatment period and values obtained at six months after completion of the treatment were taken into consideration for the evaluation. For data processing, in addition to the clinical symptoms, values of serum ALT activity, the result of the HCV-PCR test, and the histology of the liver biopsy performed at completion of the treatment were also taken into consideration. For details of the methods of examination, we refer to our previous publication [6]. Patients were informed on the particulars of the therapy before treatment, and they gave a written informed consent to the medicinal therapy in advance.

Data were analyzed by statistical methods (paired t-test). Data are expressed as mean ±SEM. P<0.05 was considered to indicate statistical significance.

**Results**

Three patients of the 12 were sustained responders, 7 patients gave a partial response, and 2 patients did not respond to the treatment (non-responders). Mild-moderate side effects, not necessitating cessation of the treatment, were observed in 6 cases. Most adverse reactions consisted of flu-like complaints (headache, weakness, muscle pain, and fever), and in individual cases moderate leucopenia, thrombocytopenia, and hemolysis of moderate degree occurred as undesired effects.

The level of the serum ALT decreased significantly in comparison to the baseline, usually after a few weeks of treatment; it often reached normal values (Figure 2), and the main ALT value remained at this level until completion of the treatment. During the follow-up period, at the 3 months’ control the main value increased significantly, but it was considerably lower than at baseline, and at the 6 months’ control we found also a reduced ALT activity. Serum aspartate-aminotransferase (AST) showed essentially similar changes (Figure 3). Gamma-glutamyl-transpeptidase (GGT) values were scattered significantly, being unsuitable for drawing definite conclusions. Serum bilirubin level was higher than normal at baseline, and during the treatment, while varying, but it usually was lower than at baseline. At six months after completion of the treatment these data were found in the normal range (Figure 4).

HCV-RNA studies gave negative results in 3 cases at completion of the treatment, and the same was observed at 6 months’ follow-up. In these cases ALT values were completely normal during the whole period studied. No rejection occurred in these patients. In seven cases the HCV-PCR examination remained positive both at completion of treatment, and at the 6 months’ follow-up, although the viral titer was reduced significantly in comparison to the baseline. The activities of ALT were in all cases lower than the baseline data. Two patients were non-responders.

Histological examination showed a close correlation with the HCV-RNA and ALT values. In the three patients with full response the findings of the control liver biopsy were negative, and in the

![Figure 2](image1.png)  *sign. vs. 0. month

**Figure 2.** Changes in the activities of alanine-aminotransferase during combined interferon-ribavirin treatment and in the follow-up period

![Figure 3](image2.png)  *sign. vs. 0. month

**Figure 3.** Changes in the activities of aspartate-aminotransferase during combined interferon-ribavirin treatment and in the follow-up period
remaining cases we observed an improvement in the Knodell-index, that is, the grading score was significantly reduced, while the staging score remained unchanged (Figure 5).

**Discussion**

In case of an infection with the hepatitis C virus, chronic hepatitis develops in 85% of the patients, and it transforms into liver cirrhosis in half of the cases in spite of the standard treatment with combined interferon and ribavirin treatment. In the end stage of the disease, liver transplantation may be the therapeutic modality. However, within 3-36 months after liver transplantation in a great part of the patients – if previous elimination of the virus has not been attained – acute hepatitis C develops that becomes chronic in most instances. If the patient received an antiviral treatment before transplantation leading to the elimination of the virus, no recurrent hepatitis develops [10]. The literary data vary concerning the efficacy of combined interferon and ribavirin treatment in patients with chronic recurrent hepatitis after liver transplantation [13-15]. Long-term complete response, with regard to all genotypes, usually can be seen in about 21% of the cases after liver transplantation, like in chronic hepatitis C [16].

In a greater study, complete response was found in 43% of HCV genotype 2-3, and in 12% of genotype 1 following conventional antiviral therapy [7]. In our current report, all patients carried the virus with genotype 1. Sustained response was observed in 3 cases out of 12 patients, that is a slightly better rate than that usually found in the literature. In Hungary, Telegdy et al. [17] reported their experience concerning the treatment of a patient with chronic hepatitis C, who underwent liver transplantation. After 6 months' treatment with combined interferon and ribavirin therapy they found a permanently low viral titer and normal ALT values with a mild hepatic fibrosis, even at 18 months after the liver transplantation.

In the treatment of chronic hepatitis C the most recent therapy is the administration of the pegylated interferon once a week, together with ribavirin treatment [8, 9]. There are two different forms of pegylated interferon, a product with a molecular weight of 12 kD (Pegintron – Schering-Plough), and another with that of 40 kD (Pegasys – Roche). Combined treatment with pegylated interferon and ribavirin in chronic hepatitis C is much more effective; a success rate of up to 75-80% in genotype 2-3, and 65-70% in genotype 1 can be attained. A complete response in 40% is possible even in cases with fibrosis of significant degree [8, 9]. This newer combination can be supposed to be more effective in chronic recurring hepatitis C following liver transplantation, as well [18, 19].

On the basis of data in the literature and our own observations, we consider the combined interferon-ribavirin treatment is advisable in chronic viral hepatitis C in the case of HCV recurrence following liver transplantation, even, if a complete remission can only be observed at a relatively low rate. Based on the most recent experiences, the combination of pegylated interferon and ribavirin therapy could be the treatment modality of choice also in patients, who underwent liver transplantation.

**References**