

## Clinical Features of Patients with Chronic Hepatitis C Before and After Antiviral Treatment

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### ABSTRACT

Hepatitis C virus (HCV) infection represents one of the unsolved problems of the contemporary medicine. It persists in the host in more than 70% of patients. About 20-25% of patients infected chronically develop cirrhosis with a risk of further primary hepatocellular carcinoma. Interferon therapy has been the most effective therapy for chronic hepatitis C. The aim of the study was the evaluation of clinical features in the patients with chronic HCV infection and comparative study of the effectiveness of treatment with alpha-interferon and pegylated interferon. Combined antiviral therapy with pegylated interferon and ribavirin is more effective than treatment with standard interferon-alpha plus ribavirin, there were fewer side effects with the first regime.

**KEYWORDS:** *chronic hepatitis C, interferon-alpha, ribavirin, sustained viral response*

**H**epatitis C virus (HCV) infection persists in the host in more than 70% of patients, inducing a chronic hepatitis C with fluctuating serum aminotransferase level and detectable serum HCV-RNA [1,3]. About 20-25% of patients infected chronically within 20 years will develop cirrhosis with a risk of further primary hepatocellular carcinoma (ca.10-15%). At most transplantation centers HCV now represents the leading cause for liver graft [8,9]. Nowadays about 170-200 million people i.e. 3% of the world population is infected with hepatitis C virus (WHO, 2002).

Pathogenic agent of the hepatitis C is a single-strand RNA virus, which belongs to the family of flaviviridae. It was first discovered by Choo and colleagues in 1989 and the disease was referred as non-A, non-B or posttransfusive hepatitis [2,7]. The viral RNA contains approximately 10.000 nucleotides. Methods of molecular biology have made it possible to identify HCV antigen structures and specific antibodies to hepatitis C virus. There are 3 structural proteins: 2 envelope and 1 nucleocapsid (core) proteins, as well as 6 nonstructural proteins.

Interferon therapy has been the most effective therapy for chronic hepatitis C. In responders to the antiviral therapy hepatitis activity becomes weak and the amount of HCV-RNA decreases or disappears. Natural course of viral hepatitis considerably depends on the host immune response in the liver. A complex cytokine network of the liver seems to regulate the activity of the hepatitis and of the viral replication. Interferon-alpha, as a cytokine that stimulates antiviral response of T-lymphocytes, represents an important component for the treatment of patients with HCV-infection [4,5]. Recently, conjugation of interferon-alpha with polyethyleneglycol (PEG) has been used to enhance the half-life of the drug and prolong its clinical efficacy [6]. With the advent of combination therapy (interferon or pegylated interferon plus ribavirin), the proportion of patients with chronic hepatitis C treated with interferon monotherapy has been substantially diminished. However there is a large population of HCV-positive patients that was treated with interferon alone and that has had a detectable HCV-RNA at the end of treatment (non-responders) or after the completion of treatment (relapsers). Currently recommended treatment for previously untreated and relapsed patients is a combination of peg-interferon and ribavirin, resulting a

sustained virological response to the therapy in approximately 50-65% of patients [10,11].

### MATERIALS AND METHODS

We have studied 168 patients with chronic hepatitis C. The diagnosis was based on clinical, laboratory and pathomorphological findings: HCV-RNA-positive blood serum, and antibodies to HCV; HCV genotype and viral load (by quantitative HCV-RNA PCR) were defined as well. Liver biopsy was performed in all cases, which provided histological confirmation of diagnosis and determined an index of the liver parenchyma inflammation grade and fibrosis stage.

The patients' age ranged between 16-65 years. Mean age was 38.5±6.5 yr. 107 (64%) were males, 61 (36%) - females.

The patients were arranged in two groups according to their treatment regimen. In I group treatment with ribavirin was combined with interferon-alpha, while the II group received pegylated interferon plus ribavirin. Mean age and male/female ratio was about the same in each group.

Virus genotype distribution in the groups was almost identical as well:

*I group:* genotype 1a and 1b - 48 patients (64%), genotype 2a and 2b - 15 patients (20%), genotype 3a and 3b - 10 patients (12%), genotype 4a - 3 patients (4%).

*II group:* genotype 1a and 1b - 63 patients (69%), genotype 2a and 2b - 14 patients (16%), genotype 3a and 3b - 10 patients (10%), genotype 4a - 3 patients (3%) and genotype 5 - 2 cases (2%).

Mean viral load in I group was 580.000±44.000 U/ml, in the II group: 690.000±48.000 U/ml.

Histological investigation of the biopsy material revealed the following degrees of fibrosis and inflammation of liver parenchyma:

*I group:* fibrosis: 0-15%, 1-43%, 2-22%, 3-15%, 4-5% inflammation of the portal area: 0-8%, 1-27%, 2-35%, 3-25%, 4-5%.

*II group:* fibrosis: 0-8%, 1-25%, 2-38%, 3-20%, 4-9%;

inflammation of the portal area: 0-9%, 1-36%, 2-40%, 3-10%, 4-5%.

There were two regimes of the treatment administered to patients: 1. interferon-alpha 2a ("Roferon-A", Hoffman-La Roche; standard dose: 6 million Units s.c. 3 times a week for the first 12 weeks, followed by 3 million Units 3 times a week for the next 36 weeks), ribavirin - 800-1200 mg/day (10mg/kg twice a day orally); 2. pegilated interferon-alpha-2b ("Peg-Intron", Essex Pharma; 1.5 (g/kg/week s.c. for 48 weeks if the genotype is 1, 4 and 5 and for 24 weeks if the genotype is 2 and 3) and ribavirin 800-1200 mg/day ("Rebetol" 10 mg/kg if the genotype is 1, 4 and 5; 800 mg twice a day orally if the genotype is 2 and 3).

The first regime of treatment was given to 76 patients (45%) and the second one to 92 patients (55%). 54% of patients complained of chronic fatigue and difficulties in concentration and memory. These patients showed evidence of cognitive impairment, primarily attention and higher levels of anxiety and depression, also impairment of quality of life. 46 % of patients have had no complains.

Shortly after the initiation of treatment the patients developed mainly flue-like side effects: malaise, tiredness, weakening, headache (80%), arthralgia and/or myalgia (ca. 60%); temperature reaction was detected in additional 25 cases. Paracetamol was administered in order to eliminate these side effects at the initial stage of treatment before the Interferon injection and, if necessary, in 24 hours after the injection (pill or suppository). Besides, impaired concentration was revealed in 21 cases (14%), transitory hair loss - in 23 cases (20%), which normalized after the termination of treatment; although these symptoms did not require the discontinuation of treatment, it proceeded in general regime and the symptoms gradually (in 2-4 weeks) disappeared. Leucopenia (<2000/ $\mu$ l), thrombocytopenia (<50.000/ $\mu$ l) or severe depression were the criteria for discontinuation of treatment [3, 8], though such cases were not involved in our study.

Sustained viral response (SVR) to antiviral therapy was considered in the cases where transaminase normalization and HCV-RNA elimination were detected in at least 6 months after the end of the treatment. Blood biochemical tests and HCV-RNA identification were carried out after 6, 16, 24, 38 and 48 weeks; these findings were also defined 6 months following to the completion of treatment to study sustained viral response.

After the treatment in the I group HCV-RNA became negative in 51% of patients, while in the II group this was documented in 67%. After 6 months from the termination of the treatment relapses have been observed. For that time sustained virological response was observed in the I group in 45% and in the II group - in 64%. Patients who failed to reach SVR did not differ by age, sex, weight or degree of hepatic inflammation/fibrosis. However they have had mostly genotype 1 and also higher viral load: HCV-RNA greater than 850000 U/ml. So these baseline characteristics associate with SVR response.

### CONCLUSIONS

1. Combined antiviral therapy with pegilated interferon and ribavirin is more effective (sustained viral response in 64 %) than treatment with standard interferon-alpha plus ribavirin (SVR in 48%); in addition there are fewer side effects and the injection is administered only once a week.
2. HCV infection with genotype 1 is characterized by aggressive course and resistance to antiviral therapy. Consequently this form requires higher doses of interferon and ribavirin and longer treatment, namely 48 weeks.
3. In the case of genotypes 2 and 3 the 24 week-treatment is sufficient and the doses of antiviral drugs are lower, namely: ribavirin 800 mg/day despite the patient's weight
4. High baseline viremia (viral load), ALT serum levels and high histological necroinflammatory score are shown as predictive resistance factors to the antiviral therapy.

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Liver enzyme	I group		P	II group		p	Normal values
	Before treatment	After treatment		Before treatment	After treatment		
ALT	118±45	24±9	p<0.05	160±46	23±5	p<0.001	<24 U/l
AST	102±32	32±10	p<0.05	111±31	23±6	p<0.001	<18 U/l
$\gamma$ -GT	101±25	34±9	p<0.01	106±29	29±6	p<0.001	<28 U/l
AP	146±24	81±11	p<0.01	268±27	156±27	p<0.01	40-170 U/l
Bilirubin (total)	1.48±0.41	0.5±0.24	p<0.05	1.59±0.18	1.0±0.11	p<0.001	0,2-1,2 mg/dl
Cholesterol	251±78	211±98	n.s.	275±69	225±86	n.s.	120-240 mg/dl
Albumin	5.4±0.5	3.9±0.2	p<0.001	5.5±0.26	4.5±0.23	p<0.001	3,5-5 g/dl
Prothrombin index	91±10	117±8	p<0.05	86±9	109±7	p<0.05	75-120%

**Tab.1** Biochemical parameters before and after treatment and their distribution according to groups.

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## Клиническая характеристика больных хроническим гепатитом С до и после антивирусного лечения

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### РЕЗЮМЕ

Вирусный гепатит С представляет собой одну из нерешенных медицинских проблем во всем мире. На сегодняшний день не существует эффективного антивирусного лечения. У многих больных хроническим гепатитом С, которые лечились традиционным препаратом Интерферон-альфа, возникает рецидив (10-18%). Целью работы являлось изучение клинической картины больных хроническим гепатитом С, а также сравнение эффективности при лечении альфа-интерфероном и пегилированным интерфероном. Обследовано 168 больных хроническим гепатитом С. Оказалось, что лечение пег-интерфероном в сочетании с рибавирином более эффективно (положительный стабильный вирусологический ответ в 64% versus 48%).

**Ключевые слова:** хронический гепатит С, интерферон-альфа, рибавирин, стабильный вирусологический ответ