

## Treatment of anicteric acute hepatitis C with peginterferon alpha-2a plus ribavirin

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**Background.** Hepatitis C virus (HCV) infection is the most frequent cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma in the world. Acute hepatitis C is the most commonly asymptomatic liver disease with the development of chronic HCV infection in the majority of infected patients. Studies of the natural history of HCV infection suggest that only 15–30% of patients with acute infection recover spontaneously. Others, up to 85% of the infected patients develop chronic hepatitis C. Acute hepatitis C is so uncommon and with the unpredictable occurrence, and of the low frequency, that it is difficult to determine the optimal treatment of this disease. There have been many randomized, controlled trials of the therapy in patients with chronic hepatitis C, but none of an adequate size or rigor in patients with acute hepatitis C. Therefore, the causal treatment of patients with acute hepatitis C aimed at the prevention of chronic liver disease is necessary. **Case report.** We have treated a patient with anicteric form of acute hepatitis C after a three-month outpatient follow-up using a combined therapy: pegylated interferon-alpha 2a, 180 µg, subcutaneously, once a week plus ribavirin 1000 mg orally once a day. The treatment lasted 24 weeks. Stable biochemical and virological response was achieved both at the end of the treatment and 6 months after the completion of the therapy. **Conclusion.** We believe that the above mentioned might be one of the approaches to the treatment of acute hepatitis C. However, further prospective studies with significantly larger number of patients are necessary for the definite conclusions about the treatment of HCV infections.

**Key words:** hepatitis C, chronic; hepacivirus; interferon-alpha; ribavirin.

### Introduction

Hepatitis C virus infection is the leading cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma. About 170 million people worldwide are estimated to be infected, and the progression from acute to chronic HCV infection occurs in 50–84% of the cases (1, 2). However, current therapies for chronic infection are not quite effective. Even the latest approach, a therapy combined with peginterferon alpha-2a or 2b and ribavirin, eliminates the virus in only 54–56% of the cases with chronic infection (3).

Considering the risk of chronic disease development, and the response rate to the treatment once chronic disease has been established, it is important to consider the treatment of acute HCV infection before it progresses to the chronic state. However, acute hepatitis C has asymptomatic course most frequently (up to 80%) that makes the diagnosis of the disease more difficult.

In general, acute HCV infection was considered to be present if at least one of the following criteria was met: known or suspected exposure to HCV within the preceding four months, documented seroconversion to positivity for antibodies against HCV, or a serum alanine aminotransferase (ALT) level of more than 600 IU/l (20 times the upper limit of the normal range), with a documented normal level during the year before the infection.

The aim of this case report was to determine whether the treatment (peginterferon alpha-2a plus ribavirin) during the acute phase could prevent the development of chronic HCV infection.

### Case report

A patient, 39-year-old Bachelor of Law from Belgrade, developed the disease abruptly, characterized by nausea, vomiting urge, the loss of appetite and blunt epigastric

and lumbar pain. Routine biochemical analyses verified the enhanced activity of serum transaminase: AST 483 IU/l, ALT 1332 IU/l. Epidemiological screening was inconclusive. Nine months before, the patient underwent biochemical blood analyses without any specific medical reason and the obtained values were within the cut-off range.

An objective examination confirmed that the patient was anicteric, the skin was free of efflorescence. The patient had hepatosplenomegaly: the liver was palpable about 1 cm below the right costal margin, with a round margin, smooth surface and tenderness on palpation; the splenic tip was palpable about 0.5 cm below the left costal margin, with no tenderness on palpation.

Echotomographic examination of the abdomen – the liver was homogenous with prominent vascular markings, with the right lobar diameters of 13.5 cm. The spleen was homogenous, 14.5 cm in size.

HCV infection was checked by the ELISA tests (Organon, Netherlands): hepatitis A virus (HAV IgM, anti-HBc total, HCV, Ortho Diagnostics, Germany) and (antihepatitis virus-HEV IgM and IgG, Genelab Diagnostics, Singapore). HIV infection was excluded by the ELISA test (Organon, Netherlands).

Serological blood examination evidenced anti-HCV positivity in the two samples obtained in the one-month interval. Serum HCV RNA level was determined using a polymerase chain reaction (PCR) method (Amplicor, Roche Diagnostics) and it was 2 306 550 copies /ml (922 620 IU/ml). The viral genotype, determined using a Line probe assay (Innogenetics, Haven, Belgium) was 3a.

Based on the same method, hepatitis B (HBsAg, anti-HBc IgM), hepatitis A (anti-HAV IgM) and hepatitis E (anti-HEV IgM) viral infections were ruled out.

The patient was outpatiently followed-up for 3 months and he was free of subjective complaints during the period. After 3 months, serum transaminase activity was still significantly increased: AST 196 IU/l, ALT 346 IU/l.

Pegylated interferon alpha-2a (PEG IFN- $\alpha$ 2a) was initiated in the dose of 180  $\mu$ g, subcutaneously, once a week, combined with ribavirin in the dose of 1000 mg, orally once a day. At the beginning of the treatment, the patient developed an expected “flu-like syndrome” with an elevated body temperature, myalgia, arthralgia, and malaise. Adverse effects of the drug were easily resolved with paracetamol. From the second month of the treatment until the end of the treatment, the patient received 135  $\mu$ g of PEG IFN- $\alpha$ 2a due to leucopenia and thrombocytopenia. Serum transferase activity was within the reference range (< 30 IU/l) from the third month of the treatment and it was maintained within the normal range throughout the treatment (6 months), as well as during the continuous follow-up over the following 6 months. HCV RNA was not detectable by the end of the treatment nor after 6-month-follow-up-period.

## Discussion

There is no standard therapy for acute HCV infection. The overarching question, of course, is whether the patients

with acute hepatitis C really need to be treated. There is little evidence that the therapy ameliorates the symptoms or shortens the course of illness. The reported rate of the progression to chronic infection may be artificially high, owing to the inaccuracy of antibody testing and to the variability in the rates of chronic infection in different populations. Lower rates of chronic hepatitis C have been reported in children, in young adults, particularly young women and in persons with jaundice. Jaeckel et al. (4) reported their experience in an uncontrolled trial in Germany with the use of a standardized 24-week course of IFN- $\alpha$  for the treatment of acute hepatitis C. The average time from the infection to the first signs or symptoms of hepatitis was 54 days, and the average time from the infection until the start of the therapy was 89 days. Of the 44 treated patients, 43 (98 %) had a sustained biochemical and virologic response, defined by the presence of normal serum ALT levels and the absence of detectable HCV RNA in serum 24 weeks after the end of the treatment.

In addition, all but one patient completed the therapy and none had an exacerbation of liver disease. These patients were treated with high doses of interferon, receiving 5 MIU daily for 4 weeks, followed by 5 MIU thrice weekly for 20 weeks. Similar results were obtained in the study by Delwaide (5), in which a high induction dose was administered.

Over the last 5 years, three different meta-analyses of the controlled trials of standard interferon alfa (IFN- $\alpha$ ) as the treatment for acute hepatitis C have shown that the treatment of patients with a low dose of IFN- $\alpha$  3 MIU three times weekly (t.i.w) for a short period (12 weeks) is significantly more effective than no treatment in obtaining a sustained virological response (6–8). In 2002, the National Institute of Health Consensus Conference on the Management of Hepatitis C stated that the minimum dose required for patients with acute hepatitis C in order to obtain a significant benefit was 3 MIU of IFN- $\alpha$  given t.i.w. for at least 12 weeks (9).

Some authors also suggested a short-term interferon therapy of acute hepatitis C.

Nomura et al. (10) treated 15 patients with acute hepatitis C. Short-term consisted of natural IFN- $\alpha$  (6 MIU) administered on consecutive days for a period of 4 weeks. This therapy was associated with a sustained virological response in 13 out of 15 patients (87%).

Although some authors have suggested that the benefit of interferon monotherapy may be higher in patients infected with HCV genotype other than 1 or in patients with low pretreatment HCV RNA levels (11, 12), other authors have not been able to confirm these observations (13, 14). Therefore, the level of accuracy sufficient to predict interferon responsiveness in the individual patients cannot be reached.

The key clinical question is whether all the patients with acute hepatitis C should immediately receive the treatment or whether the interferon therapy should be de-

layed and administered only to the subgroup of patients who might become chronically infected.

Santantonio et al. (15) observed in a prospective long-term study, that the chronicity rate was higher in asymptomatic than in symptomatic hepatitis. This prospective study clearly demonstrated that a spontaneous HCV RNA clearance occurred within 8–12 weeks from the onset of the disease. The reported value for spontaneous viral clearance was in accordance with the results of the recently published study by Gerlach (16), showing that patients with acute hepatitis C cleared the virus within the first 12 weeks.

Therefore, we initiated the therapy in our patient after 3-month outpatient follow-up, when the activity of the disease was significant as well as the number of viral copies per 1 ml of blood. Additionally, the patient had infection with 3a genotype, which leads to chronic HCV infection in a lower percent of cases. Namely, Leichmann et al. (17) evidenced that more than 90% of patients developed chronic infection if they were infected with genotype 1, that was, more than 60% if they were infected with genotype 3.

Starting from the finding that the combined therapy (IFN- $\alpha$ 2a plus ribavirin) is more efficient than monotherapy (IFN- $\alpha$ 2a) in patients with the chronic hepatitis C, several papers have been recently published on efficacy of the combined therapy in patients with acute hepatitis C, i.e., on the significance of the therapy in the prevention of the development of chronic hepatitis.

Santantonio et al. (18) presented data comparing interferon alone with interferon plus ribavirin in patients with the diagnosis of acute hepatitis C based on the documented HCV seroconversion, who continued to have high ALT levels and persistent viremia 3 months after clinical presentation. Eleven patients received interferon alone (5 MIU t.i.w. for 24 weeks and then 3 MIU thrice weekly for the additional 6 months) and 6 of the patients received interferon at a similar dosage plus ribavirin (800 or 1000 mg/day) for 12 months. The patients were followed for at least 6 months after the discontinued treatment. At the end of the therapy, normal ALT levels and undetectable HCV RNA were ob-

tained in the 10 of 11 (91%) patients treated with interferon alone and in the 5 of 6 (83%) patients treated with interferon plus ribavirin. During follow-up, 2 recipients of interferon alone relapsed after 1 and 14 months, respectively, and 1 recipient of interferon plus ribavirin relapsed after 5 months. The response was not correlated with HCV genotype, and the addition of ribavirin did not improve the end-of-treatment response.

Kamal et al. (19) reported similar results after the comparison of the efficacy of the combined therapy (PEG IFN- $\alpha$  plus ribavirin) and monotherapy (PEG IFN- $\alpha$ ). Peginterferon could be given weekly, resulting in more sustained serum levels, and consistently inducing a higher rate of response than conventional interferons. Forty subjects with the proven acute hepatitis C who received either PEG IFN- $\alpha$  plus ribavirin ( $n = 20$ ) or PEG IFN- $\alpha$  monotherapy ( $n = 20$ ) for 24 weeks were prospectively followed up. The sustained virological response rate was 85% with PEG IFN- $\alpha$  /ribavirin combination and 80% with PEG IFN- $\alpha$  monotherapy.

### Conclusion

In conclusion, recent reports have demonstrated a beneficial effect of interferon therapy in patients with acute hepatitis C. Treating all patients with acute hepatitis C is expensive. Arguments could be stated for either the wait-and-see or the immediate-therapy approach. In patients who remain viremic, interferon treatment initiated 12 weeks after clinical presentation can render a sustained virological response. The most effective treatment, including the optimal dose and duration, has yet to be determined. In general, the daily induction dose of IFN- $\alpha$  during the first month is the best therapeutic option. The potential benefit of pegylated interferon and the role of ribavirin remains challenging and the most crucial of all is the need for more information, and for more prospective studies, including the larger numbers of patients.

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### Apstrakt

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#### LEČENJE ANIKTERIČKOG AKUTNOG HEPATITISA C SA PEGINTERFERONOM ALFA-2a I RIBAVIRINOM

**Uvod.** Infekcija izazvana virusom hepatitisa C (HCV) najčešći je uzrok razvoja hronične infekcije, ciroze jetre i hepatocelularnog karcinoma u svetu. Akutna infekcija je uglavnom blaga i asimptomatska kod većine inficiranih bolesnika. Studije koje su proučavale tok ove infekcije pokazale su da svega 15–30% bolesnika spontano eliminiše infekciju, a kod ostalih inficiranih (do 85%), razvija se hronični hepatitis C. Klinički manifestna forma akutnog hepatitisa C je veoma retka i nemoguće je predvideti broj bolesnika sa akutnim hepatitisom C, te je veoma teško proučavati optimalnu terapiju za ovo stanje. S jedne strane postoji veliki broj randomizovanih, kontrolisanih studija u svetu koje su proučavale terapiju hroničnog hepatitisa C, dok nijedna takva studija nije pratila bolesnike sa akutnim hepatitisom C. Važno je naglasiti i da je kausalna terapija akutne infekcije HCV neophodna kako bi se sprečio razvoj hroniciteta. **Prikaz bolesnika.** Bolesnik sa anikteričnom formom akutnog hepatitisa C pažljivo je praćen tri meseca pre primene terapije. U terapiji je primenjen pegilovani rekombinantni interferon alfa-2a, u dozi od 180 µg, supkutano jednom nedeljno i ribavirin u dozi od 1 000 mg, oralno jednom dnevno. Bolesnik je lečen 24 nedelje, a nakon toga su praćeni virusološki i biohemijski nalazi još šest meseci. Stabilan biohemijski i virusološki odgovor zabeležen je kako na kraju primene leka, tako i na kraju perioda praćenja. **Zaključak.** Primena pegilovanog rekombinantnog interferona alfa-2a, u dozi od 180 µg, supkutano, jednom nedeljno i ribavirin u dozi od 1 000 mg, oralno, jednom dnevno je po našem mišljenju jedan od mogućih terapijski pristupa lečenju akutne HCV infekcije. Za definitivan zaključak koja je terapija najefikasnija i najsigurnija za ove bolesnike neophodno je sprovođenje prospektivne studije sa značajno većim brojem bolesnika sa akutnim hepatitisom C.

**Ključne reči:** hepatitis C, hronični; hepacivirus; interferon-alfa; ribavirin.