

Spontaneous Viral Clearance in Patients With Acute Hepatitis C Can Be Predicted by Repeated Measurements of Serum Viral Load

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Early interferon (IFN) therapy prevents viral persistence in acute hepatitis C, but in view of the resulting costs and morbidity patients who really need therapy have to be identified. Twelve consecutive patients with acute hepatitis C (9 women, 3 men, mean age: 39.5 ± 18.8 y, genotype 1: 7, genotype 3a: 3, 2 could not be genotyped) were studied. The sources of infection were medical procedures in 6, sexual transmission in 3, and intravenous drug abuse in 3 patients. Viral load was measured by Cobas Amplicor HCV Monitor v2.0 (Roche Diagnostic Systems, Branchburg, NY). The time from infection to clinical symptoms was 43.3 ± 8.6 (mean ± SD) days. Eight patients cleared hepatitis C virus (HCV) spontaneously and remained HCV-RNA negative with a follow-up of 9.0 ± 3.9 months. In these patients viral load declined fast and continuously. The time from exposure to HCV-RNA negativity was 77.4 ± 25.3 and from the first symptoms was 34.7 ± 22.1 days. In 4 patients HCV-RNA levels remained high or even increased. Two of them became sustained responders to treatment initiated after a 6-week observation period. The 2 remaining patients were not treated (one because of contraindications for IFN, the other declined therapy) and are still HCV-RNA positive. In conclusion, patients with acute icteric hepatitis C have a high rate of spontaneous viral clearance within the first month after the onset of symptoms. IFN therapy appears only needed in patients who fail to clear the virus within 35 days after onset of symptoms. By this approach, IFN therapy was not necessary in two thirds of patients with acute hepatitis C. (HEPATOLOGY 2003;37:60-64.)

Natural history of acute hepatitis C virus (HCV) infection is variable. Progression to chronic hepatitis occurs in 50% to 84% of cases.¹⁻⁹ This variation can be partly explained by the mode of transmission of HCV, viral factors, and by the ability of the host to mount a strong T-cell response to eliminate the virus. Acute HCV infection generally has a mild course, most cases are asymptomatic, and fulminant hepatic failure is very rare.^{10,11} The long-term sequelae of chronic hepatitis are the subject of ongoing discussions. Carefully con-

ducted epidemiologic studies in well-documented cases of acute hepatitis C indicate that disease follows a very mild course and that occurrence of cirrhosis within the first 25 years after infection is rare.^{2,3,7}

Treatment of chronic hepatitis C, especially in patients infected with genotype 1 or 4, is still unsatisfactory. Despite improvements in response rates, current combination therapy with pegylated interferon (IFN) alfa-2a or -2b and ribavirin for chronic hepatitis C infection yields response rates from 54% to 56%.^{12,13} Prevention of chronicity by early antiviral treatment thus may be important. Because of the infrequent nature of acute hepatitis C the impact of early antiviral therapy has not been well studied and is conflicting.¹⁴ Only in 2 of 6 controlled trials using 3 MU IFN-2b 3 times a week for 6 to 24 weeks¹⁵ eradication of HCV RNA was assessed. In general, transition to chronicity was not different from untreated controls. Only one study using 10 MU of IFN-2b until normalization of transaminase levels reported an 82% sustained virologic response.¹⁶ A recent study¹⁷ using 5 MU IFN alfa-2b for 6 months showed a 98% HCV eradication in

Abbreviations: HCV, hepatitis C virus; IFN, interferon; ALT, alanine transaminase.

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patients who received the full course of treatment. Based on these findings, the investigators concluded that early treatment with IFN-2b should be given to all patients with acute HCV infection.

However, despite this impressive result there are still a number of important unresolved issues concerning the treatment of acute HCV infection. It remains unclear whether IFN should be given to all patients with acute hepatitis C on the basis of a single, uncontrolled trial. IFN therapy is expensive and carries a substantial morbidity. For example, one could consider not treating patients with genotype 2 or 3 because these patients can be cured in almost 90% of cases by combination therapy with pegylated IFN- α and ribavirin if they become chronic.^{12,13} Furthermore, the rate of spontaneous viral clearance in symptomatic acute hepatitis C is unknown. In a recent report, 9 of 15 patients spontaneously eliminated HCV.¹⁸ Interestingly, in 3 of the patients HCV clearance occurred as late as 8 to 24 months after infection. A preliminary report has shown that 23 of 50 patients with acute hepatitis C clear the virus within the first 12 weeks,¹⁹ and IFN treatment initiated after 12 weeks from clinical presentation still achieved a 90% sustained virologic response. These findings would suggest that it is prudent to wait until 12 weeks and then consider treatment. However, it is unknown if a later initiation of therapy will yield the same favorable response rate as very early treatment. Thus, it may be unethical to wait 12 weeks when knowing that nearly all patients could be cured with immediate therapy. A way to solve this conflicting issue is to study factors predicting spontaneous viral eradication. In the present study we addressed this question by prospectively investigating HCV viremia in patients with acute hepatitis C.

Patients and Methods

Patients

In the years 2000 and 2001, all 12 patients with acute hepatitis C (8 women, 2 men, mean age: 39.5 ± 18.8 y) referred to one of the 2 participating hospitals were prospectively studied. Based on Austrian guidelines established in 1998 patients were offered antiviral treatment after an observation period of 4 weeks.

The clinical characteristics are summarized in Table 1. For various reasons 11 patients were investigated within 4 months before onset of symptoms (8 because of a planned medical procedure, in a drug addiction treatment center, at job application, before blood plasma donation, or at a routine medical examination) and tested negative for anti-HCV antibodies and had normal transaminase levels. The source of infection could be identified or suggested in all patients. Six patients were infected during medical procedures (orthopedic surgery in 4, gynecologic surgery in one, and coronary stenting in one), 3 by an infected sexual partner, and 3 were intravenous drug abusers. Three patients were infected with HCV genotype 1b, 2 with HCV genotype 1a/1b, 3 patients with HCV genotype 3a, and 2 with HCV genotype 1a. Two patients could not be genotyped because they were already HCV-RNA negative at admission.

Methods

Serum HCV-RNA Detection, Quantification, and Genotyping. All sera were stored at -80°C within 1 hour after drawing blood to achieve optimal conditions for RNA determination and quantification. Antibodies to HCV were determined by second-generation enzyme-linked immunosorbent assay. Qualitative HCV-RNA polymerase chain reaction was performed by Cobas Am-

Table 1. Patient Characteristics

Patient	Age/Sex	Mode of Infection	Days to Symptoms	Genotype	Viral Load* (IU/mL)	Bilirubin* (mg/dL)	ALT* (U/L)	HCV Clearance
A.V.	60.1/m	Med	54	1a/1b	741,000	0.84	419	No
N.U.	32.2/f	Sex	—	3a	18,100	9.57	2,005	Spontaneous
M.F.	46.5/f	Med	35	1a/1b	332	15.1	872	Spontaneous
I.M.	35.5/f	Med	43	ND	Negative	9.62	853	Spontaneous
M.M.	26.5/f	Sex	38†	3a	630	4.97	970	Spontaneous
E.T.	44.6/f	Med	42	1b	8,080	17.5	1,430	IFN
A.E.	25/f	Intravenous drugs	—	ND	Negative	7.32	1,151	Spontaneous
A.H.	20.5/f	Intravenous drugs	41†	1a	2,340	5.58	1,240	Spontaneous
H.S.	73/m	Med	53	1b	956	17.6	814	IFN
L.K.	78/f	Med	60	1b	Negative	20.1	510	Spontaneous
H.F.	21.7/m	Intravenous drugs	34†	3a	1,264,000	2.4	89	Spontaneous
J.L.	31.5/f	Sex	49†	1a	837,000	1.1	688	No

Abbreviations: Med, nosocomial infection; sex, transmission by HCV-infected partner.

*At first visit.

†Time from last illicit drug use or sexual contact to a HCV-positive partner as reported by the patients.

plicor HCV test (Roche Diagnostic Systems, Branchburg, NY). Viral load was determined by using the Cobas Amplicor HCV Monitor test, v2.0 (Roche Diagnostic Systems). Data are expressed as IU/mL. Quantitative limit of detection was 200 to 600 IU/mL. The interassay coefficient of variation of the test was 11% in the high titer range (2.1×10^4 to 1.9×10^5 IU/mL; 95% confidence interval) and 13% in the low range (1.3×10^3 to 1.2×10^4 IU/mL). Positive controls were tested in triplicate within 20 consecutive runs for determination of pooled intra- and interassay coefficients of variation.

HCV genotypes were assessed by a line probe assay (INNO-LiPA II, Innogenetics, Zwijnaarde, Belgium).

Data Presentation and Statistical Analysis. Comparisons between means were performed using the general linear model (Scheffé test as post hoc test) and Student's *t* test. The Kruskal-Wallis test was used for not normally distributed data as evaluated by the Kolmogorov-Smirnov test. A commercially available computer program (SPSS 8.0, SPSS INC., Chicago, IL) was used for all statistical calculations.

Results

The average time from infection to the first sign of symptoms of disease was 43.3 ± 8.6 days. At admission, the median serum bilirubin level was 9.6 mg/dL (range: 1.1-20.1), alanine transaminase (ALT) level was 872 U/L (89-2005; normal: <23), and alkaline phosphatase level was 270 U/L (177-440; normal: <170).

Eight patients (66.7%) cleared HCV spontaneously without antiviral therapy. In 5 there was a fast and continuous decline of HCV RNA (Fig. 1A). Two patients were already HCV-RNA negative at admission. In one patient a single qualitative HCV-RNA test obtained after 79 days of onset of symptoms was negative. Viral load was measured repeatedly in 9 patients (Fig. 1A and B). The mean time from exposure to HCV-RNA negativity was 77.4 ± 25.3 days and from the first symptoms to HCV-RNA negativity was 34.7 ± 22.1 days in the patients who cleared the virus without antiviral therapy. All patients except one showed a fast and continuous decline of serum HCV concentration (Fig. 1A). In contrast, in 4 there was either no change or even an increase in viral load (Fig. 1B). By week 4, HCV viremia was substantially higher in the 4 patients who did not clear the virus spontaneously ($P < .01$).

Initially, serum ALT levels decreased in all patients irrespective of the decline in HCV concentration (Fig. 1A and B). All patients who cleared the virus spontaneously normalized ALT levels within 49.2 ± 15.7 days, but in 6 patients ALT level was still abnormal when HCV RNA became negative (ranging between 2 \times and 6 \times the upper

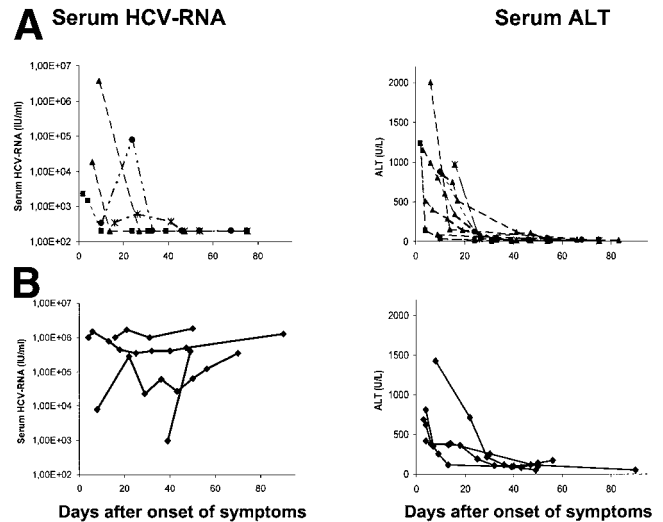


Fig. 1. (A) Time course of HCV serum concentration and of ALT level in patients with acute hepatitis C who became HCV-RNA negative without therapy. The detection level for HCV by qualitative polymerase chain reaction was 100 IU/mL. In addition, 2 patients were already HCV-RNA negative at admission and in one patient the first sample was obtained 79 days after the onset of symptoms and was negative for HCV RNA. (B) Time course of HCV serum concentration and of ALT level in the 4 patients with acute hepatitis C who did not clear HCV RNA spontaneously.

limit of normal). In contrast, ALT levels remained abnormal in the patients with ongoing viremia.

Six weeks after the onset of symptoms treatment with 1.5 μ g/kg PEG-Intron (Aesca Schering Plough, Traiskirchen, Austria)/6 mo was initiated in 2 patients. Both patients became sustained responders. The third patient had an acute attack of psychosis requiring intensive psychiatric therapy and has received no antiviral therapy so far. The fourth patient initially declined therapy but consented to a full course of IFN/ribavirin combination therapy 18 months after onset of symptoms.

The patients who developed viral persistence were older (52.3 ± 13.9 vs. 35.7 ± 17.8 , $y \pm SD$), however, this did not reach statistical significance. The baseline viral load was $396,759 \pm 227,311$ (IU/mL \pm SE) in patients with viral persistence and $171,451 \pm 66,421$ in those with spontaneous viral clearance ($P = .44$). All patients with spontaneous viral clearance developed jaundice, whereas 2 of the 4 patients with viral persistence were anicteric (Table 1).

Discussion

The results of this study indicate that repeated measurement of HCV concentration in serum is useful to identify patients with acute hepatitis C who will benefit from antiviral therapy. In contrast, serial ALT measurements within the first weeks of acute disease failed to

discriminate patients with spontaneous viral clearance from those who developed chronic viremia. Based on this approach, antiviral therapy may only be necessary in a minority of patients who seek medical attendance because of an acute icteric hepatitis C. This does not support the conclusion of the recent German study¹⁷ that, in view of a 98% response rate, all patients with acute hepatitis C should receive IFN therapy as soon as the diagnosis is made.

Our data may not be applicable to all cases of acute hepatitis C. All patients in this study were symptomatic and the majority were women. By chance, 11 of the 12 patients were either tested for HCV within 3 months before onset of jaundice or a blood sample obtained during this period was available for testing. Thus, all cases but one were documented anti-HCV negative before exposure to HCV and had unquestionable acute hepatitis. Jaundice reflects an effective elimination of all infected hepatocytes by an appropriate cell-mediated immune mechanism.⁶ Thus, the presence of jaundice may identify a group of immune-competent subjects with a more favorable outcome than patients with asymptomatic acute hepatitis C.^{20,21} It is conceivable that asymptomatic cases with only mild elevation of ALT levels may develop viral persistence due to a weak initial immune response to viral antigens.²² It is unknown whether sex affects immune response to HCV. However, there are several lines of evidence that women may clear HCV easier than men. First, female gender is a good prognostic factor in IFN-based treatments of chronic hepatitis C.²³ Second, chronic hepatitis C is more common in men than in women. In all treatment studies in Austria the men to women ratio was about 3:1.^{24,25} This difference may be due to a higher prevalence in risk behavior in men but more likely reflects a less effective immune clearance of HCV. Finally, the situation is quite similar in hepatitis B virus infection.²⁶

There is no standard therapy for acute HCV infection.²⁷ Several studies have evaluated the efficacy of IFN therapy for acute HCV infection.²⁸⁻³⁸ However, all studies have substantial limitations. The small number of patients (also in the present study) reflects the rarity of the disease. Some studies included primarily patients with asymptomatic transfusion-associated acute HCV infection.²⁸⁻³⁶ Treatment protocols were different with respect to the dose and duration of therapy. Some studies used IFN β .^{32,33} More importantly, older studies measured outcome not on the basis of viral parameters but by the normalization of ALT levels.^{29,34-36} An unknown variable is the time of initiation of therapy with respect to the onset of symptoms or the time of infection. In the German study,¹⁷ the time from exposure to treatment was 89 days (mean, with a range of 30-112 d). In the present

study, the mean time from infection to spontaneous viral clearance was 77 ± 25 days. Thus, the majority of the patients in the German study still had the propensity to achieve a spontaneous viral clearance.

In summary, these preliminary data indicate that patients with symptomatic acute hepatitis C may not need immediate antiviral therapy. Our data suggest that a follow-up of at least 30 days is required to identify those patients who should receive treatment. The role of early antiviral therapy in acute hepatitis C should be investigated by a prospective multicenter study that should include only patients who do not clear the virus spontaneously.

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