

CLINICAL—LIVER, PANCREAS, AND BILIARY TRACT

Acute Hepatitis C: High Rate of Both Spontaneous and Treatment-Induced Viral Clearance

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See editorial on page 253.

Background & Aims: Acute hepatitis C virus infection accounts for approximately 20% of cases of acute hepatitis today. The aim of this study was to define the natural course of the disease and to contribute to the development of treatment strategies for acute hepatitis C virus. **Methods:** The diagnosis of acute hepatitis C virus in 60 patients was based on seroconversion to anti-hepatitis C virus antibodies or clinical and biochemical criteria and on the presence of hepatitis C virus RNA in the first serum sample. **Results:** Fifty-one of 60 (85%) patients presented with symptomatic acute hepatitis C virus. In the natural (untreated) course of acute symptomatic hepatitis C (n = 46), spontaneous clearance was observed in 24 patients (52%), usually within 12 weeks after the onset of symptoms, whereas all asymptomatic patients (n = 9) developed chronic hepatitis C. The start of antiviral therapy (interferon- α with or without ribavirin) beyond 3 months after the onset of acute hepatitis induced sustained viral clearance in 80% of treated patients. **Conclusions:** The management of acute hepatitis C has to take into account the high rate of spontaneous viral clearance within 12 weeks after the onset of symptomatic disease. Treatment of only those patients who remain hepatitis C virus RNA positive for more than 3 months after the onset of disease led to an overall viral clearance (self-limited and treatment induced) in 91% of patients, and unnecessary treatment was avoided in those with spontaneous viral clearance. Patients with asymptomatic acute hepatitis C virus infection are unlikely to clear the infection spontaneously and should be treated as early as possible.

transmission,^{1,2} acute HCV (aHC) infection is still responsible for approximately 20% of cases of acute hepatitis, and approximately 30,000 new cases occur every year in the United States alone.³

The most important risk factor for HCV infection today is intravenous drug abuse, but in up to 40% of cases, the exact mode of HCV transmission remains undefined. Worldwide at least 170 million individuals are chronically infected with HCV and, lacking awareness of infection, could further contribute to continuing HCV transmission.

So far, most studies on aHC have focused on posttransfusion hepatitis,⁴⁻¹⁰ which runs a clinically asymptomatic course in 50%–80% of patients. Symptomatic aHC, however, may have a better outcome,^{11,12} but detailed information on the prognostic parameters and correlates of immunity are still lacking. Although acute liver failure is rare, up to 85% of infected patients develop chronic HCV infection, with a significant long-term risk of liver cirrhosis and hepatocellular carcinoma.¹³ Today only a few patients with aHC are found incidentally, whereas the vast majority are identified only if symptoms compatible with acute hepatitis are present or if an infection is suspected and follow-up examinations show increased aminotransferases. Compared with patients in prospective studies of posttransfusion HCV infection, these patients differ with regard to patient characteristics, mode of transmission, and comorbidity and have not yet been enrolled in controlled studies.

Hepatitis C virus (HCV) was discovered in 1989 as the principal cause of posttransfusion non-A/non-B hepatitis. Although subsequent screening of blood products for HCV has virtually eliminated this mode of

Abbreviations used in this paper: aHC, acute hepatitis C virus; IFN, interferon; PEG-IFN, pegylated interferon.

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Given the risk of a chronic course of HCV infection, with its associated morbidity and mortality, the clinical management strategy has to take into account the natural course of symptomatic aHC and the response to antiviral therapy, bearing in mind the considerable side effects and costs of current HCV treatment strategies. We therefore studied 60 patients with aHC as it presents to the physician today to define its natural course and to contribute to the identification of the optimal time point to start treatment.

Materials and Methods

Patients

Sixty consecutive patients (35 women and 25 men) with aHC were diagnosed in 2 large referral centers for infectious diseases and hepatology (Medical Department II, Klinikum Großhadern, Munich, Germany, and General Hospital München Schwabing, Munich, Germany) from January 1, 1993, to July 31, 2000, and received antiviral treatment after informed consent was obtained. Most patients (51 of 60) presented with symptomatic acute hepatitis. The most likely source of HCV infection was determined in an initial patient interview that explored the incubation period for possible sources of HCV transmission, e.g., new intravenous drug abuse (Table 1).

Diagnosis

The diagnosis of aHC was based on seroconversion to anti-HCV antibodies (44 of 60 patients) and/or clinical and biochemical criteria (acute onset of hepatitis in individuals without preexisting liver disease, exclusion of other coexisting infections, metabolic or toxic liver disease, and increases of alanine aminotransferase [ALT] at least 10 times the upper limit of normal) and on the presence of HCV RNA by reverse-transcription polymerase chain reaction in the first serum sample ($n = 60$).

Serological Tests and Seroconversion

Serum samples were tested for the presence of anti-HCV antibodies by second-generation enzyme immunoassay (EIA 2.0; Ortho-Clinical Diagnostics, Raritan, NJ). Antibodies against distinct viral antigens were assessed by Western blot by using recombinant antigens (Recomblot HCV[®]; Mikrogen, Munich, Germany). HCV RNA was assessed by polymerase chain reaction and was quantified by Amplicor Monitor (Hoffmann-La Roche, Basel, Switzerland). HCV genotyping was performed by analyzing amplicons from the conserved 5' untranslated region generated by nested polymerase chain reaction as described elsewhere.¹⁴

De novo seroconversion with the appearance of anti-HCV antibodies in second-generation enzyme-linked immunosorbent assay was shown in 29 patients. In 15 patients, antibodies in the enzyme-linked immunosorbent assay were positive or

Table 1. Patient Characteristics in Self-Limited and Chronic Course of Acute Hepatitis C

Variable	Acute hepatitis C		P value
	Self-limited	Chronic	
No. of patients	24	36	
Age at onset of symptoms (yr)			
Median/mean	36/35.7	35/35.4	0.88
Range	17-55	17-63	
Sex			
Male	6	19	
Female	18	17	0.034
Suspected source of infection			
Unknown	7	7	0.83
Sexual	3	3	0.83
Medical procedures	8	12	0.83
Intravenous drugs	5	10	0.83
Needlestick	1	4	0.83
Seroconversion			
ELISA	8	21	0.38
Immunoblot	8	7	0.38
None	8	8	0.38
Genotype (Simmonds)			
1a	4	8	0.58
1b	8	16	0.58
2a/b	0	3	0.58
3	5	6	0.58
4	0	2	0.58
Unknown	7	1	0.58
Peak ALT			
Median (U/L)	828	671	0.15
Mean (U/L)	964 ± 469	837 ± 593	
Peak bilirubin			
Median (mg/dL)	7.9	2.5	0.14
Mean (mg/dL)	9.03 ± 5.58	6.92 ± 7.96	
Time (wk) until			
Normalization of ALT	9.9		
Range	2.9-26.5		
HCV RNA negative	7.3		
Range	1.0-21		

ELISA, enzyme-linked immunosorbent assay.

indeterminate. In these samples, immunoblot analysis showed single reactivities against viral antigens (anti-HCV NS3, $n = 7$; anti-HCV core, $n = 2$; anti-HCV NS3/NS4, $n = 1$; and anti-HCV core/HCV NS3, $n = 5$) in the initial serum. During follow-up, a change in the serological profile, with an increasing number of reactivities against further HCV antigens, was noted in all 15 patients, indicating seroconversion after acute infection¹⁵ (Figure 1).

Follow-up

After the diagnosis of aHC was established, patients were seen by a gastroenterologist in the outpatient clinic every 7 to 14 days in the first 2 months, at monthly to bimonthly intervals until month 6, and every 3 to 6 months thereafter. Physical and biochemical examinations were performed at each presentation. Patients were followed up for a median of 24 months (range, 7-70 months). A self-limited course of aHC

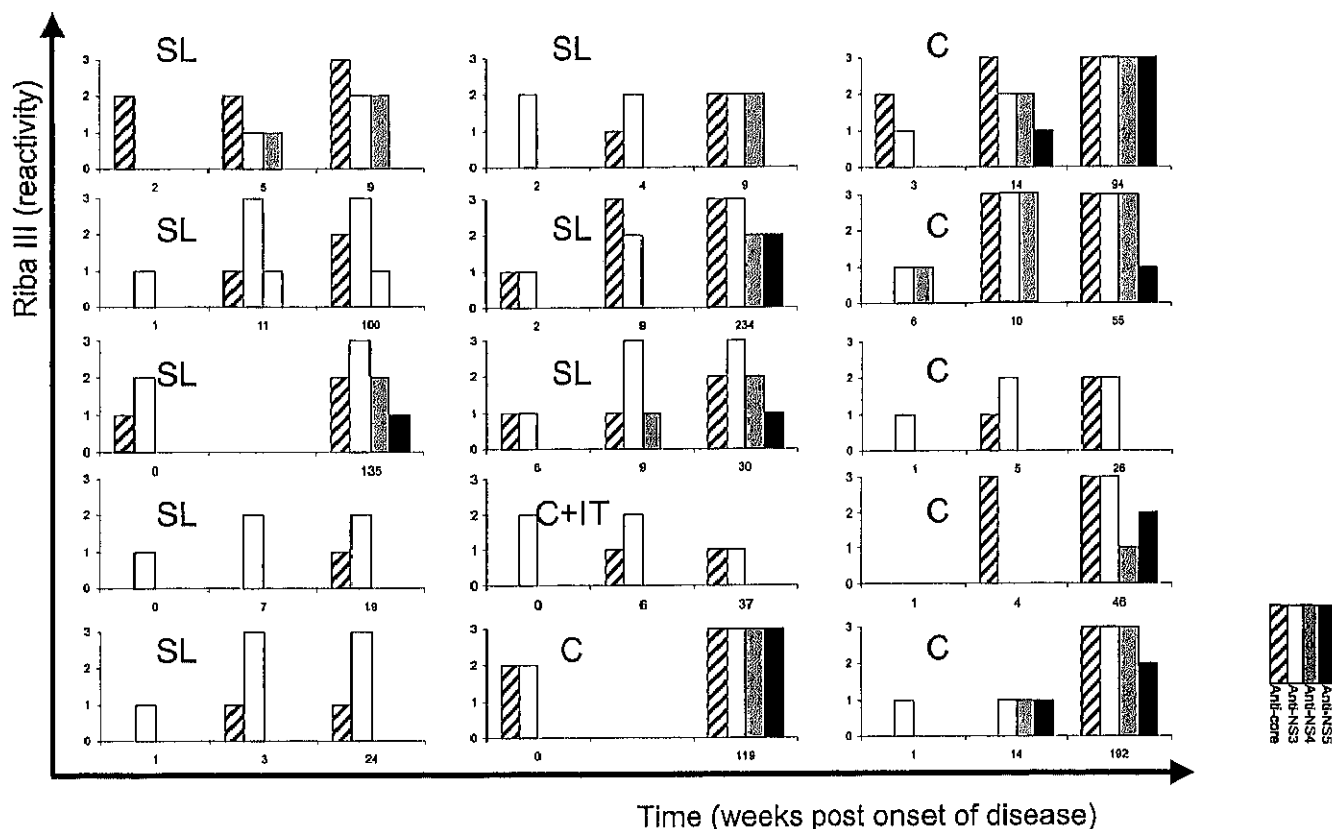


Figure 1. Immunoblot reactivities against HCV proteins. Analysis was performed during follow-up of acute HCV. After reactivities against single HCV antigens were found in the initial phase of acute hepatitis, an increasing number of reactivities against different antigens developed during follow-up, indicating acute infection. SL, patients with spontaneous HCV elimination and a self-limited course; C(+IT), patients with chronic evolution of HCV (and immediate treatment); Riba, ribavirin.

was defined as permanent (>6 months) loss of HCV RNA in serum and normalization of ALT. Patients with transient loss or persistence of serum HCV RNA beyond 6 months after the onset of symptoms or/and biochemical signs of hepatitis were considered as having chronic HCV.

Antiviral Therapy

Once the diagnosis of aHC was confirmed, therapeutic options were discussed with the patients to obtain informed consent for further treatment. Antiviral therapy was commenced immediately after the diagnosis of aHC was established in 6 patients: patients were treated with interferon (IFN)- α monotherapy ($n = 2$) or in combination with ribavirin ($n = 3$) or with pegylated (PEG)-IFN- $\alpha 2a$ ($n = 1$). In most patients ($n = 20$), treatment was started during follow-up when a self-limited course of aHCV was deemed unlikely (median start of therapy, 5.7 months; range, 0–26 months). Untreated patients ($n = 10$; Figure 1) refused therapy ($n = 2$), were lost to follow-up ($n = 4$), or were not eligible for IFN- α or combination therapy because of continued intravenous drug abuse ($n = 2$), osteomyelitis ($n = 1$), or severe coronary heart disease ($n = 1$).

Patients received the most effective antiviral regimen available at the time: standard IFN- α therapy (3 to 5 MIU 3 times

a week) alone ($n = 10$) or in combination with ribavirin ($n = 10$) and PEG-IFN alone ($n = 2$) or in combination with ribavirin ($n = 4$). PEG-IFN and ribavirin were adjusted to weight. Therapy was initiated 0–26 months (Table 2) after the onset of symptoms. Because of transient loss to follow-up, 5 patients were treated 12 months after the onset of disease.

Statistical Analysis

Results are presented as original data, means, and medians. Comparisons of patients with a self-limited course vs. a chronic course of disease were performed with the Mann-Whitney ranked sum test (median) and with Fisher exact tests (frequencies) with Yates corrections. P values of less than 0.05 were considered significant. Odds ratios with a 95% confidence interval were calculated with the Mantel-Haenszel method. As statistical software, SAS 6.01 was used for evaluation (SAS Institute, Cary, NC).

Results

Patient Characteristics

In this study, 60 patients (35 women and 25 men) with aHC were enrolled (Table 1 and Figure 2). In most

Table 2. Patients With Acute Hepatitis C Infection and Antiviral Treatment

Patient No.	Possible mode of infection	Symptoms (icteric)	Genotype (Simmonds)	Treatment	Interferon dosage	Start of treatment (mos)	Duration of IFN- α treatment (wk)	Cumulative dosage (MU)	Outcome
Sustained responder									
25	Unknown	Yes (yes)	3	IFN	3 MU TIW	1.0	35	31.1	SR
26	IV drug abuse	Yes (yes)	1b	IFN	5 MU/3 MU TIW	26.2	52	469	SR
27	Proctoscopy	No	1b	IFN	5 MU/3 MU TIW	9.7	38	574	SR
28	Unknown	Yes (yes)	1b	IFN, IFN/ribavirin	5 MU TIW	10.0	61	91.1	SR
29	Unknown	Yes	3	IFN	5 MU TIW	12.6	50	656	SR
30	Coronary angiography	No	3	PEG-IFN	100 μ g qw	12.9	46		SR
31	Sexual	Yes (yes)	1b	IFN	3 MU TIW	2.4	29	261	SR
32	IV drug abuse	No	3	IFN	5 MU TIW	7.6	34	512	SR
33	IV drug abuse	Yes (yes)	3	IFN/ribavirin	5 MU TIW	6.5	50	745	SR
34	IV drug abuse	Yes (yes)	uk	IFN, IFN/ribavirin	3 MU TIW	1.0	52	467	SR
35	Unknown	Yes (yes)	2a	IFN/ribavirin	3 MU TIW	7.1	52	784	SR
36	Needlestick	No	1a	IFN/ribavirin	5 MU TIW	5.9	53	793	SR
37	Sexual	Yes (yes)	1a	IFN/ribavirin	5 MU TIW	5.5	26	383	SR
38	IV drug abuse	Yes (yes)	1b	IFN/ribavirin	3 MU TIW	4.2	50	454	SR
39	Needlestick	Yes	1b	IFN/ribavirin, PEG/ribavirin	5 MU qd, 100 μ g qw	0.3	51		SR
40	IV drug abuse	No	2a	PEG-IFN/ribavirin	80 μ g qw	6.6	23		SR
41	Surgery	Yes (yes)	3b	PEG-IFN/ribavirin	80 μ g qw	1.9	25		SR
42	Dental operation	Yes (yes)	1a	IFN/ribavirin	5 MU TIW	3.7	26	388	SR
43	Needlestick	No	1b	IFN/ribavirin	5 MU TIW	0	26	386	SR
44	IV drug abuse	Yes (no)	1b	PEG-IFN/ribavirin	80 μ g qw	3.4	14		SR
45	Unknown	Yes (yes)	1b	IFN	5 MU TIW	0.9	17	255	SR
Relapse and nonresponse									
46	Coronary angiography	No	1a	PEG-IFN	80 μ g qw	0.4	36		Relapse
47	Sexual	Yes	1a	IFN	3 MU TIW	8.6	37	330	Relapse
48	Bypass operation	Yes	1b	IFN	3 MU TIW	20.5	31	276	NR
49	Surgery and transfusion	Yes	4	IFN	3 \times 6 MU	3.3	26	470	NR
50	Unknown	Yes (yes)	1a	IFN/ribavirin	3 MU TIW	11.6	23	211	NR

TIW, 3 times a week; qw, once a week; qd, every day; SR, sustained response; IV, intravenous; NR, no response.

infected individuals, ALT and bilirubin peaked at the time of presentation; an initial increase of ALT and bilirubin at the beginning of the disease was followed by a rapid decline of ALT in the first weeks of follow-up. Although 9 patients were diagnosed with asymptomatic aHC, most (85%) patients presented with symptomatic disease. Symptoms included jaundice (68%); nausea (34%); dark urine and white stool (39%); abdominal pain, mostly in the right upper quadrant (25%); and flu-like symptoms (55%; Table 3). Asymptomatic patients were diagnosed during routine testing after needlestick injury ($n = 2$), during follow-up examinations for coronary heart disease ($n = 2$) or osteomyelitis ($n = 1$), during repeated proctoscopic procedures ($n = 1$), or during examinations due to drug abuse ($n = 2$). The major risk factors for aHC were intravenous drug abuse ($n = 15$), recent hospitalization or medical procedures ($n = 20$), HCV-positive sexual partner ($n = 6$), and needlestick injury in medical employees ($n = 5$); in

14 patients (23%), no risk factor or potential source of infection could be identified.

Natural Course

Six of 60 patients received immediate antiviral therapy (IFN- α alone or in combination with ribavirin). Thus, in 54 patients who were not treated immediately, the natural course of aHC was further studied: 37 (68%) patients initially cleared the virus spontaneously within a mean of 8.4 weeks (range, 1–26 weeks), but only 24 (44%) persistently remained HCV RNA negative until the end of follow-up (median, 27 months; range, 6–55 months) and were classified as having self-limited HCV. In 13 of 54 patients (24%), HCV RNA relapsed after a median of 18.1 weeks (range, 8–86 weeks), and 17 (31%) patients did not clear HCV infection spontaneously and developed chronic HCV infection.

Patients with self-limited aHC ($n = 24$) and those who developed chronic HCV infection ($n = 30$) did not

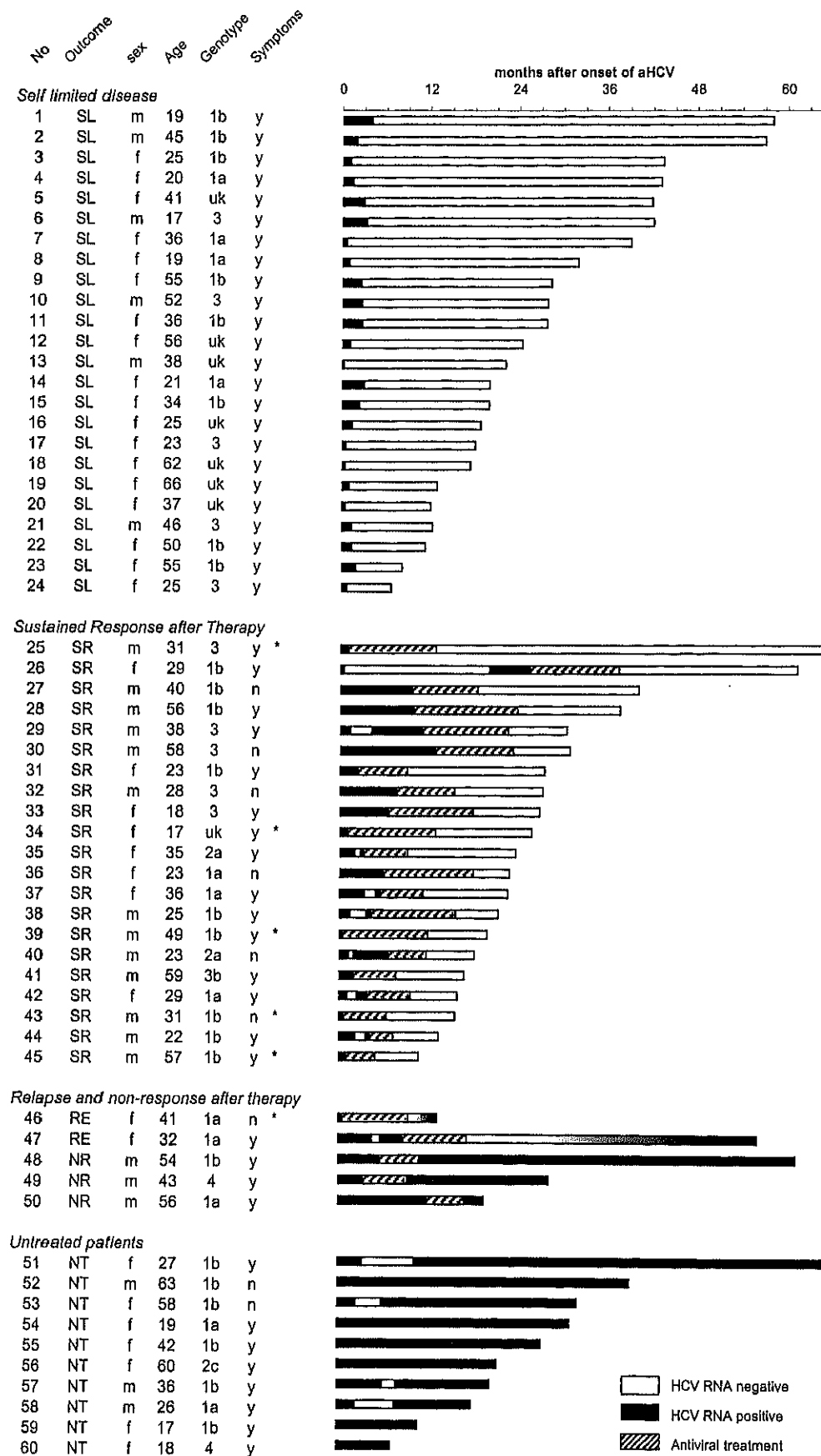


Figure 2. Each patient was characterized by outcome, sex, age, genotype, and presence of symptoms at the onset of disease. Patients are sorted by outcome: SL, patients with spontaneous HCV elimination and a self-limited course; SR, sustained viral clearance (>6 months) after antiviral treatment; RE, relapsing hepatitis; NR, nonresponder to antiviral therapy; NT, untreated patients; uk, genotype unknown. Bars indicate length of follow up, presence (closed bars) vs. absence (open bars) of HCV RNA in serum, and antiviral treatment (hatched bars). The genotype of HCV is categorized according to classification by Simmonds. Symptoms at the onset of disease comprised fatigue, abdominal pain, jaundice, and nausea. *Immediate antiviral therapy.

Table 3. Symptoms in Acute Hepatitis C

Symptoms at presentation	Self-limited hepatitis, n (%)	Chronic evolution, n (%)	P value	Odds ratio (95% CI)
Jaundice	21/24 (87)	20/34 (59)	0.02	4.9 (1.3-18.5)
Nausea/vomiting	8/20 (40)	11/35 (31)	0.5	1.45 (0.46-4.6)
Dark urine/white stool	9/22 (41)	11/33 (33)	0.6	1.38 (0.4-4.3)
Abdominal pain (right upper quadrant)	5/21 (24)	9/33 (27)	1.0	0.8 (0.2-3.0)
Flulike symptoms	21/24 (87)	16/34 (47)	0.002	7.8 (2.2-28.7)

CI, confidence interval.

differ with regard to age, risk factors for HCV infection, HCV genotype, or initial viral load (Figure 3). However, symptomatic onset of disease and female sex were significantly associated with a self-limited course of HCV infection (Table 1). Although 24 of 46 (52%) patients with symptomatic aHC cleared the infection spontaneously, none of the patients with asymptomatic aHC ($n = 9$) lost HCV RNA without treatment ($P = 0.007$, spontaneous viral clearance in symptomatic vs. asymptomatic aHC).

Women were significantly more likely to achieve viral clearance than males ($P = 0.034$). Although this was not statistically significant, patients in the self-limited group had higher ALT and bilirubin levels. The distribution of genotypes in both groups was not statistically different (genotype in self-limited vs. chronic course, respectively: genotype 1a, 4 vs. 8; genotype 1b, 8 vs. 16; genotype 2a/b, 0 vs. 3; genotype 3, 5 vs. 6; and genotype 4, 0 vs. 2; genotype was not determined in 8 patients with self-limited infection and 2 with chronic infection). Ge-

notype 1a/1b was most frequent in both groups (self-limited, 50%; chronic, 60%). In the self-limited group, 7 patients could not be genotyped because of lack of material before viral elimination or loss of follow-up.

Antiviral Therapy

Although in 6 patients antiviral therapy was commenced immediately, 20 patients with chronic HCV started antiviral therapy with IFN- α alone or in combination with ribavirin (Table 2), usually after 3 to 6 months after the onset of symptoms. Twenty-one of 26 (81%) patients were sustained responders (loss of HCV RNA and normalization of aminotransferases >6 months after end of treatment: immediate therapy, $n = 5$; delayed start of treatment, $n = 16$). In 2 patients, HCV RNA relapsed after cessation of therapy: 1 had been treated immediately after the onset of aHC with PEG-IFN monotherapy, whereas the second had received IFN monotherapy (3 MIU 3 times a week) 8 months after symptomatic disease. Three patients (6%) were nonresponders to IFN monotherapy ($n = 2$) or combination therapy ($n = 1$; Tables 2 and 4). Ten patients were not treated (see Antiviral Therapy in Materials and Methods).

Discussion

In this study we showed that in symptomatic aHC, more than 50% of patients spontaneously and

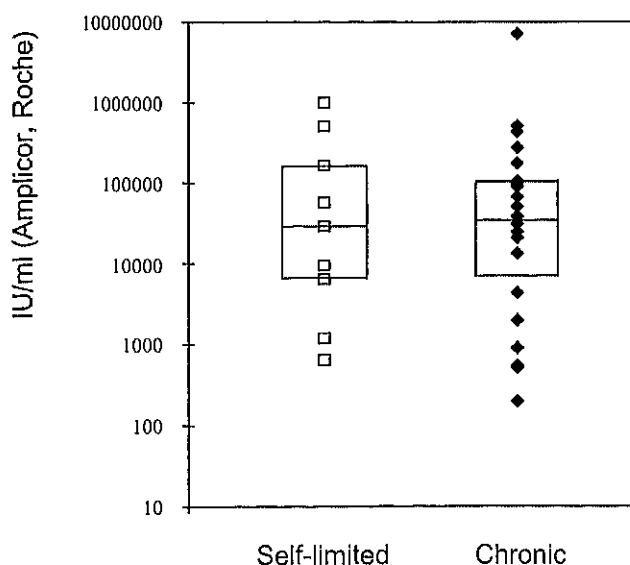


Figure 3. Quantitative HCV RNA in the first serum sample in aHC. HCV RNA was assessed by Amplicor Monitor (Hoffmann-La Roche, Basel, Switzerland). The initial viral load had no effect on the course of aHC, i.e., self-limited vs. chronic course.

Table 4. Natural Course and Immediate Treatment in Symptomatic and Asymptomatic Patients

Variable	Natural course— delayed start of treatment (symptomatic/ asymptomatic)	Immediate treatment (symptomatic/ asymptomatic)
Self-limited acute hepatitis C	24 (24/0)	—
Sustained response to antiviral therapy	16 (10/6)	5 (5/0)
Nonresponse to antiviral therapy	4 (4/0)	1 (0/1)
No treatment	10 (8/2)	—

permanently clear HCV infection within the first 3–4 months after the onset of symptoms. If patients with persistent viremia beyond that time period were treated with IFN- α monotherapy or in combination with ribavirin, 80% achieved a sustained biochemical and virological response, leading to a possible cure of 91% of patients with symptomatic aHC infection.

aHC may be asymptomatic in up to 80% of patients, but today predominantly symptomatic cases are diagnosed. The disease then is usually mild, and fulminant liver failure is very rare; thus, its propensity for chronicity remains the major threat of aHC infection today. Chronic HCV, however, is a major cause of liver cirrhosis, liver failure, and hepatocellular carcinoma and is the leading indication for liver transplantation in the Western world, and antiviral treatment with IFN- α and ribavirin in chronic HCV leads to a sustained viral clearance in only approximately 30%–54% of patients.^{16–18}

Although the pathogenesis of neither acute nor chronic HCV infection is completely understood, acute self-limiting HCV infections undoubtedly do occur, indicating that the principal feasibility to cure infection is most likely by the host's immune system. Mechanisms contributing to viral persistence could include an inefficient antiviral T-cell response,^{19–21} the high rate of viral mutations and the evolution of complex quasi-species,²² and the interaction of viral proteins with various intracellular host proteins.

Spontaneous elimination of HCV has been observed in the first few months of virus–host interaction, but once chronic infection is established, spontaneous viral clearance is exceptional. Thus, the initial months after infection seem to be of crucial importance for the subsequent course of disease. The rate of viral mutations is supposed to be particularly high in the first months after disease onset, leading to sequence evolution²³ and cytotoxic CD8⁺ epitope mutations.²⁴ Our group and others showed the importance of an antiviral CD4⁺ T-helper cell^{25,26} and a CD8⁺ cytotoxic T-cell response²⁷ during the initial phase of disease to clear the infection and thereafter to prevent viral recurrence.^{20,28}

The high percentage of spontaneous viral clearance in symptomatic patients in our cohort raises the question for the optimal treatment strategy: immediate treatment to clear the virus as early as possible or a delayed start of antiviral treatment for those patients remaining HCV RNA positive when spontaneous clearance is unlikely to be achieved. Only a few studies on the clinical response to antiviral treatment in aHC are available, and most of these were uncontrolled studies with conflicting therapeutic results,^{6–8} but they generally yielded sustained

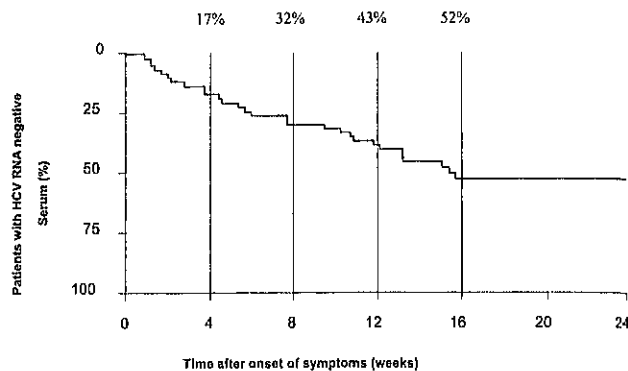


Figure 4. Spontaneous HCV clearance from the serum of patients with symptomatic aHC. Spontaneous HCV clearance was highest during the first weeks of acute hepatitis but was never observed beyond 17 weeks after the onset of symptoms.

response rates well above those expected for chronic HCV.^{4,5,9,29,30} Jaeckel et al.³¹ recently reported excellent results (sustained response of 95%) with starting treatment of patients with aHC immediately (within 4 to 16 weeks after infection) in a 1-arm treatment trial with an IFN- α induction regimen for 24 weeks, and the authors suggest immediate treatment of every aHC. However, this study was uncontrolled, and the start of therapy preceded the time of spontaneous viral clearance that was observed in our study (see comments^{32,33}).

Most of our patients with a self-limited course of infection lost HCV RNA within the first 12 weeks after the onset of symptoms, and no spontaneous viral clearance was observed after more than 16 weeks (Figure 4). Antiviral treatment of those with persistent viremia beyond 3 months after the onset of symptoms resulted in a sustained viral elimination in 80% of treated patients. Although most treated individuals did not receive the best currently available antiviral regimen, i.e., PEG-IFN- α in combination with ribavirin, spontaneous and IFN- α -induced HCV RNA clearance resulted in an overall viral elimination of 91% in symptomatic aHC. This is statistically comparable to immediate therapy for all patients but avoided unnecessary treatment of those with self-limited disease.

The question of whether immediate treatment of all patients with aHC is superior to our strategy of delayed treatment only in patients with chronic evolution could be answered by a randomized, controlled study. However, given the high rate of overall viral clearance in our study cohort, which may further improve by the general use of PEG-IFNs, there remains little space for further improvement. Moreover, immediate treatment of all patients would result in unnecessary treatment with potential complications, adverse effects, and considerable costs in 50% of patients with symptomatic disease. Finally,

some patients will have relative contraindications to antiviral treatment, and the risks and benefits of treatment then have to be balanced carefully.

Our results suggest that in the clinical management of symptomatic aHC, it is reasonable to observe patients for 3 months after the onset of symptoms and to offer antiviral treatment to all patients with persistent viremia. Follow-up is mandatory even after initial spontaneous viral clearance because recurrence and subsequent development of chronic HCV may occur. Persistent and relapsing viremia in aHC show an excellent response to antiviral treatment. In contrast to patients with symptomatic aHC, those with asymptomatic disease have little chance of spontaneous viral clearance and should receive immediate antiviral treatment.

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