Outcomes and Treatment of Acute Hepatitis C Virus Infection in a United States Population

KATHLEEN E. COREY,* ANDREW S. ROSS,‡ ALYSSE WURCEL,‡ JULIAN SCHULZE ZUR WIESCH,§ ARTHUR Y. KIM,§ GEORG M. LAUER,§ and RAYMOND T. CHUNG‡

*Medical Services, ‡Gastrointestinal Unit, and §Partners AIDS Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

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Background & Aims: Acute hepatitis C infection progresses to chronic infection in up to 80% of infected persons. Reports from Europe indicate that early treatment of acute hepatitis C infection produces sustained virologic response rates as high as 80%–98%. However, the outcome of acute hepatitis C infection in United States cohorts is not well-characterized. **Methods:** We describe the clinical course of 28 episodes of acute hepatitis C infection in 24 persons at our institution. **Results:** Of the 28 infections, 7 episodes resolved spontaneously. Of the remaining 21 episodes, 16 were treated, and 5 did not receive treatment. Of the 16 treated episodes, 4 received interferon and ribavirin, 11 received pegylated interferon and ribavirin, and 1 was treated initially with interferon monotherapy followed by pegylated interferon monotherapy. Among those episodes treated with interferon, 3 of 4 experienced sustained virologic response. Among those episodes treated with pegylated interferon, all 12 achieved SVR. In total, 15 of 16 treated patients (94%) experienced SVR. In all, 18 of the 24 patients (75%) experienced spontaneous or treatment-induced sustained virologic clearance. **Conclusions:** Our experience with treated and untreated acute HCV infection is comparable to that observed in Europe. Patients treated with antiviral therapy had an excellent response. Randomized trials to investigate immediate versus delayed treatment of acute hepatitis C infection are warranted. In view of these strongly positive outcomes, increased vigilance for acute hepatitis C becomes essential.

Recent estimates have indicated that up to 2% of the population in the United States (U.S.) is infected with hepatitis C virus (HCV).[1] Chronic HCV infection is the most common cause of chronic hepatitis worldwide, and cirrhosis attributable to HCV infection is the leading indication for liver transplantation.

Although the prevalence of chronic HCV infection is of epidemic proportion, the incidence of acute HCV infection has declined during the past 20 years. This decrease has been attributable to the successful screening of blood products for HCV, decreases in injection drug use, and improved aseptic technique. Despite these advances, an estimated 40,000 cases of acute HCV occur annually in the U.S.[2]

Untreated, acute HCV infection progresses to chronic infection in 50%–80% of patients,[3–5] whereas the remainder appear to be able to clear the virus on their own. Several studies have suggested that female sex, symptomatic disease, and high peak bilirubin levels are the strongest predictors of spontaneous viral clearance.[6] Data with regard to antiviral therapy for acute HCV infection have been difficult to interpret, primarily because of small sample sizes and lack of randomization. A meta-analysis in 1999 found that treatment with interferon alfa-2b (IFN) at doses of at least 3 MIU thrice weekly for a minimum of 12 weeks was superior to no treatment in terms of normalization of transaminases and sustained virologic response (SVR) rates.[6]

A recent study from Germany observed that 43 of 44 patients (98%) with acute HCV treated with 5 million units of IFN daily for 4 weeks followed by 5 mIU thrice weekly for 20 weeks experienced SVR.[4] Another report described SVR in 90% of patients treated with IFN alone or in combination with ribavirin (RBV).[5] Gerlach et al[6] recently observed that in a cohort of 60 patients presenting with acute HCV infection, 52% of symptomatic patients and 0% of asymptomatic patients achieved spontaneous viral clearance. In addition, among those who remained viremic, initiation of antiviral therapy with IFN monotherapy 12 weeks after the onset of acute hepatitis produced an SVR rate of 80%.[6]

European studies describing the treatment of chronic HCV infection usually report higher rates of SVR than do studies performed in North America. This has been attributed in part to the higher prevalence of the more treatment-responsive viral genotypes 2 and 3 in Europe. To date, there have been no reports describing the natural history and treatment of acute HCV infection in the U.S. Here we describe the clinical course of 24 patients with 28 episodes of acute HCV diagnosed at our institution.

Methods

Patients

The clinic charts and electronic medical records of patients diagnosed with acute HCV during the period from 1998–2005 were reviewed. The following data were recorded: age, sex, probable exposure date and type of exposure, HCV infection risk factors, human immunodeficiency virus infection status, symptoms, peak ALT, peak bilirubin, the presence of antibody

Abbreviations used in this paper: ALT, alanine aminotransferase; ETVR, end of treatment virologic response; HCV, hepatitis C virus; IDU, intravenous drug user; IFN, interferon alfa-2a/2b; MSM, men who have sex with men; PEG-IFN, pegylated interferon alfa-2a/2b; RBV, ribavirin; SVR, sustained virologic response; tiw, three times per week; U.S., United States.

1542-3565/06/$32.00
doi:10.1016/j.cgh.2006.06.026

to HCV, HCV genotype, HCV RNA, antiviral therapy, doses, duration, and complications. In some patients in whom viremic sera were not available for genotyping, serotyping for HCV genotype was performed by using the Murex HCV Serotyping 1–6 assay (Abbott, Wiesbaden, Germany) according to the manufacturer's instructions. Informed consent was obtained from all patients, and institutional review board approval was obtained. Patients were excluded if they had incomplete charts.

Acute Hepatitis C Virus Infection

The diagnosis of acute HCV infection was made if a patient presented with (1) a documented anti-HCV seroconversion with positive HCV RNA; (2) a positive anti-HCV with detectable HCV RNA and an ALT elevated to greater than 10× the upper limit of normal and a history of recent high-risk exposure; or (3) a negative anti-HCV with a positive HCV RNA.

Antiviral Therapy

At the clinician's discretion, patients were treated with standard IFN-alfa-2b at doses between 9–42 mIU weekly or pegylated interferon alfa-2a (PEG) at a dose of 180 μg weekly. In addition, most patients received combination therapy with RBV at doses of 1000–1200 mg daily on the basis of body weight less than or greater than 75 kg. The duration of therapy varied by individual patient.

Virologic Response

Patients were classified as having an end of treatment virologic response (ETVR) if they had an undetectable HCV viral load by qualitative assay at the end of treatment. An SVR was defined as an undetectable HCV RNA by qualitative assay 24 weeks after the cessation of any course of therapy.

Results

Patients and Exposure

Twenty-four patients (15 female/9 male) were diagnosed with a total of 28 discrete episodes of acute HCV between February 1998–June 2005 (Table 1). None of the patients were excluded for incomplete records. The patients ranged in age from 15–63 years (mean, 34 ± 13). Risk exposures for HCV infection included injection drug use in 13 patients, needlestick injuries in 5 patients, blood transfusions in 1 patient, shared razors in 1 patient, and unprotected sex in 1 patient. Three patients who were diagnosed with acute HCV had no clearly identifiable exposure. The median duration of follow-up was 90 weeks (range, 10–187 weeks).

Signs and Symptoms

The following were reported as initial symptoms: fatigue (n = 5), fever (n = 4), nausea (n = 8), abdominal pain (n = 3), rash (n = 1), and myalgias (n = 1). Six patients reported jaundice as the initial sign of HCV infection; 2 patients were completely asymptomatic.

Liver Tests, Viral Load, and Genotype

All 24 patients reviewed had abnormal serum ALT levels at initial presentation. Four women had discrete marked ALT elevations after exposures on 2 separate occasions, resulting in a total of 28 discrete acute infections. The mean peak ALT was 1649 ± 1454 U/L. The total bilirubin was elevated in 17 (60%) patients, with a mean peak total bilirubin of 4.4 ± 4.6 mg/dL. The mean initial HCV RNA was 325,590 ± 453,534 IU/mL (reference range, <600–700,000 IU/mL), with a median value of 63,149 ± 15,787 IU/mL. Viral genotype or serotype was identified in 27 (96%) of the 28 infections. Twenty-three (82%) infections were genotype 1, four (14%) were genotype 2 or 3, and 1 was neither genotypeable nor serotypeable. Of note, all 4 patients with multiple episodes had infections with discordant subtypes (1a and 1b).

Disease Course and Treatment

Of the 24 patients, 5 (20%; 4 female, 1 male) cleared 7 episodes of HCV infection spontaneously (Figure 1). Three of these presented twice with symptoms of acute hepatitis after discrete exposures. Of these patients, 2 spontaneously cleared viremia both times; the third was treated with PEG-IFN after the first episode and spontaneously cleared the second episode. All 5 were injection drug users and had elevated bilirubin levels and ALT levels greater than 1000 U/L at presentation. Of the 7 acute episodes with HCV that cleared spontaneously, 6 were genotype 1 and 1 was unknown. For those patients who were not treated immediately and who experienced spontaneous clearance, time from the onset of symptoms to viral clearance ranged from 10–96 days (median, 49 days).

Fifteen patients (62.5%) received antiviral therapy for 16 episodes of acute HCV infection (Table 2). One patient (patient 24) experienced 2 discrete acute infections after documented exposure to injection drug use and was treated twice. Initial therapy was with IFN ± RBV in 4 patients and PEG-IFN ± RBV in 11 patients. One patient (patient 9) who relapsed after treatment with IFN monotherapy (patient was on hemodialysis) was subsequently treated with PEG-IFN monotherapy. Therapy was initiated at a median of 21 days (range, 14–183 days) after symptoms were reported. The mean weekly dose (where known) of IFN was 26 ± 5.9 mIU, and the mean cumulative dose of IFN was 101.25 ± 206.6 mIU. The mean weekly dose of PEG-IFN was 180 μg, and the mean cumulative dose of PEG-INF was 3600 μg. The mean daily dose of RBV was 944 ± 87.5 mg. The mean duration of therapy was 30.7 ± 12 weeks.

All 15 treated patients had an ETVR. The mean week 12 $\log_{10}$ HCV RNA decline was 4.79 ± 1.23 in treated patients. All patients cleared HCV RNA by week 12. Two patients who had ETVR experienced a relapse of HCV infection. Of these, one patient (patient 7) is currently viremic and has elected not to be retreated. The other patient (patient 9) was on hemodialysis, relapsed after receiving standard IFN, and successfully achieved SVR with PEG-IFN monotherapy. Of note, this patient then underwent a living-related kidney transplant complicated by hyperacute rejection and muromonab (OK73) treatment. Despite this, she has remained HCV RNA negative for 4 years. All patients have completed treatment, and all achieved ETVR. Overall, 15 of the 16 episodes (94%) resulted in SVR.

Taken together, of the 28 acute HCV episodes, 22 resulted in spontaneous or treatment-induced SVR, and 6 resulted in persistent viremia. Of these 6 viremic patients, 5 were not treated. All 5 had absolute or relative contraindications to therapy (3 active drug users and 2 with severe depression). Of the 24 patients in all, 18 (75%) experienced sustained virologic clearance, and 6 remain viremic.