Predictors of spontaneous viral clearance and outcomes of acute hepatitis C infection

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Background/Aims: This study evaluated the predictors of spontaneous viral clearance (SVC), as defined by two consecutive undetectable hepatitis C virus (HCV) RNA tests performed ≥12 weeks apart, and the outcomes of acute hepatitis C (AHC) demonstrating SVC or treatment-induced viral clearance.

Methods: Thirty-two patients with AHC were followed for 12-16 weeks without administering antiviral therapy.

Results: HCV RNA was undetectable at least once in 14 of the 32 patients. SVC occurred in 12 patients (37.5%), among whom relapse occurred in 4. SVC was exhibited in 8 of the 11 patients exhibiting undetectable HCV RNA within 12 weeks. HCV RNA reappeared in three patients (including two patients with SVC) exhibiting undetectable HCV RNA after 12 weeks. SVC was more frequent in patients with low viremia than in those with high viremia (55.6% vs. 14.3%; P=0.02), and in patients with HCV genotype non-1b than in those with HCV genotype 1b (57.1% vs. 22.2%; P=0.04). SVC was more common in patients with a ≥2 log reduction of HCV RNA at 4 weeks than in those with a smaller reduction (90% vs. 9.1%, P=0.001). A sustained viral response was achieved in all patients (n=18) receiving antiviral therapy.

Conclusions: Baseline levels of HCV RNA and genotype non-1b were independent predictors for SVC. A ≥2 log reduction of HCV RNA at 4 weeks was a follow-up predictor for SVC. Undetectable HCV RNA occurring after 12 weeks was not sustained. All patients receiving antiviral therapy achieved a sustained viral response. Antiviral therapy should be initiated in patients with detectable HCV RNA at 12 weeks after the diagnosis. (Clin Mol Hepatol 2014;20:368-375)

Keywords: Acute hepatitis C; Spontaneous viral clearance; Interferon; HCV RNA

INTRODUCTION

World Health Organization estimates that 130 to 170 million people are chronically infected with hepatitis C virus (HCV) and at risk of developing liver cirrhosis, liver cancer, or both. More than 350,000 people die from HCV-related liver diseases every year. HCV is transmitted by parenteral routes, mainly contaminated blood products and other percutaneous exposures such as injection drug use, contaminated medical equipment, tattoos, acupuncture, maternal transmission, sexual contact and occupational exposure to blood products.

Since the 1990s, the incidence of acute hepatitis C (AHC) infection has decreased because of routine screening of blood donors. Nevertheless, newly diagnosed AHC infection cases were reported at 0.3 cases per 100,000 people in US. Considering underestimated asymptomatic infections, the incidence of AHC infection might be higher.

During the natural course of ACH, about 50-80% of AHC pa-
patients progressed to chronic hepatitis and remaining 20-50% of AHC patients showed spontaneous viral clearance (SVC) without treatment. Interferon-based antiviral therapy of AHC showed high rates of sustained virological response (SVR), defined by undetectable HCV RNA for 6 months after cessation of antiviral therapy, ranging 75-94% independent of HCV genotypes. It is important to predict the individuals who will spontaneously clear the HCV infection in order to avoid unnecessary antiviral treatment, while promptly initiating antiviral therapy to achieve high SVR for those who have a high risk for chronic hepatitis C (CHC).

The benefit of SVR after interferon-based antiviral therapy in CHC is well-documented. However, little data are available if spontaneous or treatment-induced viral clearance is sustained in patients with AHC. Therefore, this study was to analyze the predictive factors for SVC and to evaluate the outcomes in patients with spontaneous or treatment-induced viral clearance.

**MATERIALS AND METHODS**

We retrospectively analyzed 32 patients with AHC between April 2004 and December 2011. AHC was defined as (1) seroconversion from anti-HCV-negative to anti-HCV-positive with a previously negative anti-HCV test result within a year; (2) presence of HCV RNA in serum of a previous anti-HCV-negative patient.

History of exposure to possible risk factors (transfusion, invasive procedures, surgery, needle stick injury, sexual contact, tattoos, acupuncture) within 6 months before the onset of AHC was investigated by the means of a structured questionnaire at the time of first visit to each clinic.

After diagnosis of AHC was confirmed, the patients were followed at 2-4 week intervals without antiviral treatment. If SVC, defined by two consecutive undetectable HCV RNA ≥12 weeks apart, occurred, the patients were followed at 3-6 month intervals thereafter. If SVC did not occur within 12-16 weeks, we requested interferon-based antiviral therapy. In a patient whose HCV RNA progressively decreased without SVC within 3-4 months (patient 23), antiviral therapy was delayed.

The serial liver function tests, including serum albumin, bilirubin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), were performed using standard assays. Anti-HCV antibodies were determined at baseline and if the anti-HCV test was negative, the tests were repeated during the follow-up by using commercially available AxSYM kits (Abbott Diagnostic, Chicago, IL). Quantitative detection of HCV RNA was measured by COBAS Amplipcr HCV test (Roche Molecular Systems, Pleasanton, CA; lower detection limit, 50 IU/mL) or COBAS TaqMan HCV test (Roche Molecular Diagnostics; lower detection limit, 15 IU/mL) since December 2009. HCV genotyping was performed using direct sequencing.

**Statistical analysis**

Data analysis was performed using SPSS version 12.0 (SPSS Corp, Chicago, IL, USA). The differences between the categorical variables were analyzed by a chi square test. A logistic regression analysis was used to identify independent predictive factors associated with SVC. P-values less than 0.05 were considered significant.

**RESULTS**

Baseline characteristics of the 32 patients are presented in Table 1 and 2. The mean age of the patients was 46.8 years (range, 3-77 years) and 18 patients (56.3%) were male. The suspected routes of AHC were as follows: occupational needle stick injury (n=4), transfusion (n=2), sexual (n=1), operation (n=2), acupuncture (n=1), and hemodialysis (n=1). However, no potential source of infection could be found in 21 patients (65.6%).

Most patients (28/32) had symptoms at the time of diagnosis. The usual symptoms of AHC were nausea, anorexia, fatigue, right upper abdominal discomfort, malaise, fever and jaundice. In 28 (88%) of the 32 patients, baseline level of ALT was elevated more than 5 times the upper limit normal (ULN). In 23 (72%) of 32 patients, ALT was elevated more than 10 times the upper limit normal (ULN) and an elevation of bilirubin (≥2 mg/dL) was observed in 15 patients at the time of diagnosis. During short-term follow-up, serum levels of ALT was elevated more than 5 times the upper limit normal in all patients except one.

Of the 32 patients with AHC, 17 (53.1%) patients were infected with genotype 1b, followed by 2a (n=12), 2b (n=2) and 3a (n=1). Fourteen patients (43.7%) were anti-HCV negative at initial clinical presentation. Among these patients, 10 patients showed anti-HCV seroconversion and the remaining 4 patients showed persistent anti-HCV negative without relapse at the end of follow-up.

After diagnosis of AHC, the patients were followed for 6-116 months. The clinical outcomes of the patients who were followed