Rate of Sustained Virologic Response in Relation to Baseline Hepatitis C Virus (HCV) RNA Level and Rapid Virologic Clearance in Persons with Acute HCV Infection

Barbara H. McGovern,[1,2] Ellen H. Nagami,[1,5,6] Christopher E. Birch,[1,5,6] Melinda J. Bowen,[6,7] Laura L. Reyor,[3,6] Raymond T. Chung,[3,4] and Arthur Y. Kim[4,5,6]

[1]Lemuel Shattuck Hospital, Jamaica Plain, [2]Tufts Medical School, [3]Gastrointestinal Unit, Massachusetts General Hospital, [4]Harvard Medical School, and [5]Harvard University Center for AIDS Research, Boston, [6]Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology, and Harvard University (formerly known as Partners AIDS Research Center), Charlestown, and [7]University of Massachusetts Medical School, Worcester, Massachusetts

Treatment of acute hepatitis C virus (HCV) infection leads to a sustained virologic response (SVR) in the vast majority of patients, although the clinical predictors of these favorable responses are not well understood. In chronic infection, the most potent predictor of a SVR is complete viral suppression after 4 weeks of treatment, also known as a rapid virologic response (RVR). However, few patients with HCV genotype 1 infection and high-level viremia ever achieve this benchmark. In 2 separate cohorts of patients with acute HCV infection, we demonstrate that rapid virologic clearance and low-level viremia (HCV RNA level, <400,000 IU/mL) are highly prevalent, regardless of HCV genotype.

In patients with acute hepatitis C virus (HCV) infection, overall sustained virologic response (SVR) rates are much higher than those seen in patients with chronic infection, although the clinical predictors of these favorable outcomes are not well understood. In patients with chronic infection, the recent identification of rapid virologic clearance (defined as undetectable HCV viremia after 4 weeks of therapy) has been lauded as the single most important factor in determining treatment outcomes [1, 2]. The ability to achieve rapid virologic clearance is governed by 2 primary factors, namely, the infecting genotype and the level of the patient's viremia before treatment [3, 4].

RVR is attained by approximately two-thirds of patients with HCV genotype 2 or 3 infection treated with pegylated interferon plus ribavirin [5]. In contrast, this benchmark is achieved in only the minority of patients (16%–23%) with genotype 1 infection [1]. These data support the clinical observation that patients with genotype 2 or 3 infection have significantly higher overall sustained virologic response rates, compared with genotype 1–infected patients. In addition to genotype, lower levels of viremia are also strongly correlated with virologic suppression. However, only a minority of patients with chronic HCV infection have low levels of viremia (ie, <400,000 IU/mL) at baseline [4, 5].

In patients with acute HCV infection, virologic responses after 4 weeks of treatment have not been well-defined. Our goal was to assess the prevalence of RVR responses to pegylated interferon and ribavirin therapy among patients in 2 separate cohorts who received a diagnosis of acute HCV infection. We demonstrate that rapid virologic clearance is common during treatment for acute HCV infection, regardless of genotype, and that rapid virologic clearance may be related to the high prevalence of low level viremia in persons with newly acquired infection.

Patients and methods. We assessed 4-week HCV RNA responses among patients in 2 separate cohorts who were treated for acute HCV infection. The first cohort was identified prospectively beginning in October 2006 through the Massachusetts Department of Corrections. Within a week after admission to the correctional system, inmates were screened for a history of recent-onset injection drug use (IDU) and prior HCV testing. During the initial physical examination at 2 correctional intake sites, brief interviews of 3248 inmates were conducted by healthcare providers from the University of Massachusetts Healthcare Services. Of these inmates, 141 HCV-naive individuals who had a high risk for HCV infection were further screened by history and laboratory evaluation (eg, symptoms/signs of acute hepatitis, HCV seroconversion, elevations of aminotransferase levels to >7 times the upper limit of normal, and presence of HCV RNA). After diagnosis of acute HCV infection,

Received 20 February 2009; accepted 14 April 2009; electronically published 12 August 2009.

Potential conflicts of interest: B.H.M. is on the speaker's bureau of Roche Pharmaceuticals. R.T.C. receives research grant support from Roche Labs and Schering-Plough. All other authors: none reported.

Financial support: National Institutes of Health/National Institute of Allergy and Infectious Diseases (Hepatitis C Cooperative Center grant U19AI066345, grant K23 AI054379 to A.Y.K., and Harvard University Center for AIDS Research grant P30AI060354).

Presented in part: 59th Conference of the American Association for the Study of Liver Diseases, San Francisco, CA, 1 November 2008 (abstract 90-2008).

Reprints or correspondence: Dr. Barbara McGovern, Div. of Infectious Diseases, Lemuel Shattuck Hospital, 170 Morton St., Jamaica Plain, MA 02130 (bmcgovern@tuftsmedicalcenter.org).

The Journal of Infectious Diseases 2009; 200:877–81

0022-1899/2009/20006-0007$15.00
DOI: 10.1086/605444

Table 1. Demographic Characteristics and Treatment Outcomes for Patients with Acute Hepatitis C Virus (HCV) Infection

Patients, by cohort	Age, years	Sex	Ethnicity	HCV genotype	Pretreatment HCV RNA level, IU/mL	Treatment weeks	Virologic response	
							Rapid	Sustained
Incarcerated								
Patient 1[a]	21	M	White	1a	363,000	22	Yes	Yes
Patient 2	31	M	White	1a	22,200	24	Yes	Yes
Patient 3	29	M	White	1a	93,699	25	Yes	Yes
Patient 4	25	F	White	2b	1,665,560	15	Yes	Yes
Patient 5	34	M	White	1a	252,532	24	Yes	Yes
Patient 6	41	M	White	4a	88,574	24	Yes	Yes
Patient 7	29	M	White	3a	834,400	26	Yes	Yes
Patient 8	35	M	White/Hispanic	1a	32,366	16	Yes	Yes
Patient 9	24	M	White	1a	261,437	24	Yes	Yes
Patient 10	19	F	White	1a	131,819	24	Yes	Viral breakthrough
Patient 11	32	M	White	1a	546,478	20	No	Viral breakthrough
Patient 12	30	M	White	4acd	1590	16	Yes	Lost to follow-up
Patient 13	24	F	White	3a	190,778	12	Yes	Lost to follow-up
Patient 14	39	M	White	3a	93,185	12	Yes	Yes
Patient 15[b]	40	M	White	1a	1,790,000	28	Yes	No
Community								
Patient 16	63	F	White	1	95,800	12	Yes	Yes
Patient 17	36	M	White	1b	1230	24	Yes	Yes
Patient 18	20	F	White	1a	235,000	24	Yes	Yes
Patient 19	26	F	White	1a	648	24	Yes	Yes
Patient 20	20	M	White/Black	1ab	>700,000	48	No	Yes
Patient 21	27	M	White	1	292,000	24	Yes	Lost to follow-up
Patient 22[c]	29	M	White	1	>700,000	48	Yes	Yes
Patient 23	20	F	White	1	>700,000	24	Yes	Yes
Patient 24	40	F	White	3a	>700,000	12	Yes	Yes
Patient 25[c]	41	M	Hispanic	3a	1385	24	Yes	Yes

NOTE. Versant HCV RNA 2.0 (Bayer Diagnostics) was used to monitor HCV RNA levels for all patients, unless otherwise indicated.

[a] HCV RNA monitoring was performed using bDNA Quantiplex (Chiron) at all time points.

[b] A 48-week course of therapy was recommended after the patient delayed treatment for 27 months because of depression. The patient self-discontinued treatment after 27 weeks with subsequent virologic rebound.

[c] Seropositive for HIV.

we evaluated the HCV RNA level at baseline, 4 weeks, and 10 weeks and offered therapy only to patients with persistent viremia, based on our previously established screening protocol [6]. Full details of our diagnostic approach are described elsewhere [7].

Patients with viremia that persisted for >10 weeks from the time of diagnosis were offered 24 weeks of treatment with pegylated interferon alfa2b and ribavirin (800 mg daily for patients infected with genotype 2 or 3 and weight-based ribavirin therapy [13 mg/kg] for those infected with genotype 1). Patients with low-level viremia (HCV RNA level, <10,000 IU/mL) at week 10 underwent additional testing at week 14 to determine possible late clearance before initiation of treatment. Those who were administered combination therapy for persistent viremia had virologic monitoring performed with Versant HCV RNA 2.0 (Bayer Diagnostics) on a monthly basis until clearance was documented. HCV RNA was also assessed at the end of treatment and at the 6-month mark after discontinuation of therapy. HCV genotype was determined by Versant-LiPA HCV 2.0.

In the second cohort, we retrospectively reviewed 68 records from community-dwelling patients who received a diagnosis of acute HCV infection at a tertiary care center (Massachusetts General Hospital [Boston, MA]) from 1997 through 2007. Serial HCV RNA samples (mean, 5.4 samples/patient) were obtained to measure the HCV RNA level; the timing and frequency of sample collection were at the discretion of the 2 practitioners who provided care for these patients. The mean duration of sampling before treatment initiation was 17.6 weeks. From the overall cohort, 27 patients were treated for persistent viremia (6 patients were initially described in a previous report [8]. We selected 10 patients who had HCV RNA

testing performed with the Cobas Amplicor HCV Monitor after 4 weeks of pegylated interferon and ribavirin for inclusion in this report.

All study subjects with acute HCV infection gave written informed consent for observational studies of the virologic, immunologic, and clinical courses of infection. These protocols conform to the 1975 Helsinki guidelines for the conduct of human research and were approved by each hospital's institutional review board. For incarcerated subjects, the Lemuel Shattuck Hospital Human Research Review Committee includes a prisoner advocate.

Results. We identified 25 patients with acute HCV infection and persistent viremia who underwent combination therapy with pegylated interferon and ribavirin and had week 4 viral load testing performed. Fifteen patients were identified prospectively from the prison-based cohort, and 10 were identified retrospectively from the community-based cohort (table 1). Seventeen were men, and the mean age was 31 years. A total of 22 patients were white, and 1 was Hispanic; 1 person reported both white and African American ethnicity, and 1 reported both white and Hispanic ethnicity. Risk factors for HCV acquisition included IDU (for 20 patients) and sexual transmission (for 4 patients); the route of acquisition was unknown for 1 patient. Two patients in the community cohort were known to be HIV seropositive. No new diagnoses of HIV infection were made.

Nineteen patients were infected with HCV genotype 1 ($n = 17$) or 4 ($n = 2$), whereas 6 patients were infected with genotype 2 ($n = 1$) or 3 ($n = 5$). The mean HCV RNA level at enrollment was 329,210 IU/mL (range, 1004–1,745,260 IU/mL), whereas the mean HCV RNA level before treatment had increased to 391,747 IU/mL (range, 1385–1,665,560 IU/mL), although this trend was not statistically significant. Pretreatment low-level viremia was documented in 17 (68%) of 25 patients, including 12 (70.6%) of 17 with genotype 1 infection.

Rapid virologic clearance was achieved in 23 of 25 patients overall, including 2 patients with a history of HIV infection. The RVR rate was 89.5% (17 of 19) for patients infected with genotype 1 or 4 and 100% (6 of 6) for patients infected with genotype 2 or 3. On the assumption that treatment failure occurred in 3 patients who were lost to follow-up, the overall response rate was 72% (18 of 25) (figure 1).

The patients were treated for a mean duration of 22.8 weeks (range, 12–48 weeks); 1 patient was offered 48 weeks of therapy because of delayed therapeutic intervention secondary to uncontrolled depression. Adverse events were typical of combination therapy and included severe fatigue (for 5 patients), headache (for 4), loss of appetite (for 2), and new onset hypothyroidism (for 1). One patient received a single dose of erythropoietin because of anemia, and no patients required growth factors for neutropenia. Virologic breakthrough was documented in patients 10 and 11, both of whom had genotype 1 infection. Patient 10 stated that, during the last 2 months of ribavirin therapy, she had been poorly adherent. Although patient 11 was adherent to treatment, other factors may have contributed to his suboptimal response. These factors included a dramatic viral load increase between enrollment and pretreatment (from 22,635 to 546,478 IU/mL), as well as a marked increase in body weight from baseline obesity. A fasting insulin level and a glucose concentration were normal at the time of treatment discontinuation.

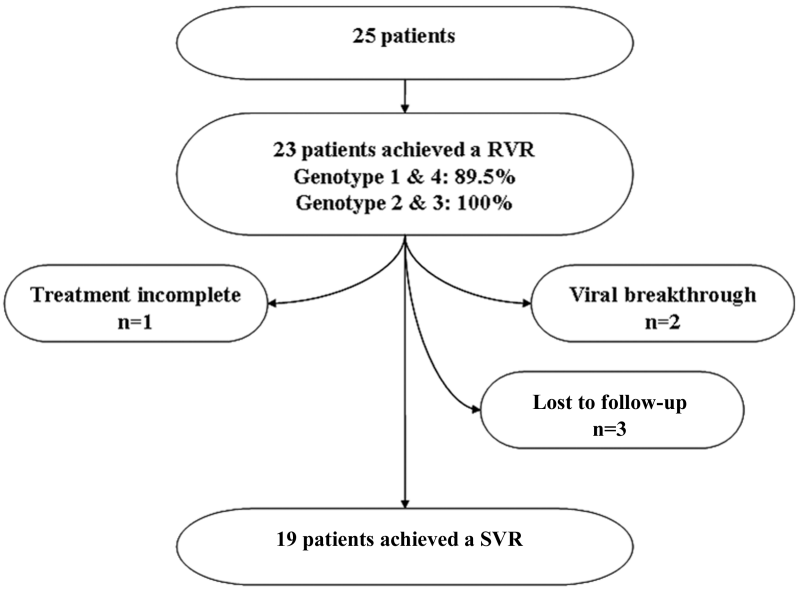

Figure 1. Treatment outcomes for 25 patients with acute hepatitis C virus infection. Eighteen of 19 patients who achieved a sustained virologic response (SVR) also achieved a rapid virologic response (RVR).

Discussion. Treatment for acute HCV infection led to rapid virologic suppression in nearly all patients, regardless of genotype. Of the 17 patients with genotype 1 infection, 88.2% achieved rapid virologic clearance. This observation is in marked contrast to the low RVR rates of 16%–23% seen in persons with chronic HCV genotype-1 infection [1].

Studies involving patients with chronic HCV infection have demonstrated that low-level viremia (<400,000 IU/mL) and RVR are strongly linked. However, low-level viremia is distinctly uncommon among persons infected with the most difficult-to-treat genotypes. For example, in one retrospective study of 1550 HCV genotype 1–infected patients who were treated with pegylated interferon alfa-2a/ribavirin, only 13% met this criterion [4]. Low-level viremia, which is distinctly uncommon in HIV/HCV-coinfected patients, also informs RVR and ultimate clinical outcomes in this difficult-to-treat patient population [9].

In contrast to chronic disease, antiviral therapy leads to a sustained virologic response in the vast majority of patients with acute HCV infection [10]. The much higher RVR rates that are seen in acute HCV infection may be linked to prevalent low-level viremia, as demonstrated in our cohort of patients with acute infection. The only patient in the incarcerated cohort who did not attain a RVR had >1 log-fold increase in viremia (>500,000 IU/mL) before treatment; one may hypothesize that he may have had a better outcome with earlier initiation of therapy at the time of lower viremia. The change in viral set point to higher levels may signal a transition from acute to chronic HCV infection with onset of T cell immune dysfunction [11]. In this setting, treatment with an immunomodulatory agent (eg, interferon) may be less effective, particularly in patients infected with genotype 1. In contrast, the level of viremia may not be as important in patients infected with an HCV genotype (ie, genotype 2 or 3) that is more responsive to interferon.

Whether low-level viremia in acute infection is reflective of immunologic containment is unknown; patients with acute infection may have some relevant cellular responses, even if viremia persists [11, 12]. During acute infection, when acquired immunity is most likely to be detected, early treatment appears to facilitate a favorable balance between host-virus dynamics. In contrast, low-level viremia may be distinctly uncommon in chronic infection because of the loss of immunologic control, as suggested by in vitro data [13, 14]. Virally induced signaling pathways (through interferon regulatory factor 3) that are favorable to the host may be abolished over time through inactivation of interferon-responsive genes (such as the gene encoding RIG-1) [13]. Moreover, the serine protease of HCV has recently been found to cleave signaling molecules essential to innate immunity [14]; the exact in vivo timing of activation of viral evasion mechanisms is currently under investigation. Thus, acute-phase HCV may represent an immunologically favorable state before the virus has escaped from both innate and acquired immunity. Acute-phase HCV is also associated with less diversity and complexity of an individual's HCV quasispecies, which in the chronic phase has also been associated with favorable treatment outcomes [15]. The contribution of the immune system may be particularly important when administering the currently available antiviral therapies, which target upregulation of general antiviral genes rather than specific HCV viral proteins [16].

Limitations of the current study include the small number of patients with acute HCV infection; thus, our observations should be confirmed by others. One strength of our study is the large representation of injection drug users, who are often underrepresented in treatment studies of HCV infection. Furthermore, we were able to demonstrate the feasibility of treating acute HCV infection in the correctional setting.

In summary, in patients with acute HCV infection, rapid virologic clearance rates are commonly observed and are closely associated with SVR, regardless of genotype. High rates of RVR appear to be closely linked to low levels of viremia, which are more common in acute HCV infection. This virologic parameter may be particularly important in genotype 1–infected patients, who have generally lower rates of SVR in response to treatment.

Acknowledgments

We especially thank the individuals who consented to take part in this study, and we are grateful to Arthur Brewer and Warren Ferguson (University of Massachusetts Medical School Correctional Health) and to the providers at MCI-Framingham and MCI-Concord for their support.

References

1. Jensen DM, Morgan TR, Marcellin P, et al. Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alpha-2a (40 kd)/ribavirin therapy. Hepatology **2006**; 43:954–60.
2. Ferenci P, Fried MW, Shiffman ML, et al. Predicting sustained virological responses in chronic hepatitis C patients treated with peginterferon alfa-2a (40 KD)/ribavirin. J Hepatol **2005**; 43:425–33.
3. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med **2002**; 347:975–82.
4. Rodriguez-Torres M, Sulkowski M, Chung RT, Hamzeh FM, Jensen DM. Association of pretreatment and on-treatment factors with rapid virologic response in HCV genotype 1–infected patients treated with peginterferon alfa-2a/ribavirin [abstract #1305]. In: Program and abstracts of the American Association for the Study of Liver Diseases, Boston, MA, 2–6 November 2007.
5. Shiffman ML, Suter F, Bacon BR, et al. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. N Engl J Med **2007**; 357:124–34.
6. McGovern B, Wurcel A, Kim AY, et al. Acute hepatitis C virus infection in incarcerated injection drug users. Clin Infect Dis **2006**; 42:1663–70.
7. McGovern BH, Birch CE, Bowen MJ, et al. Improving the diagnosis

of acute hepatitis C infection using expanded viral load criteria. Clin Infect Dis **2009** (in press).
8. Corey KE, Ross AS, Wurcel A, et al. Outcomes and treatment of acute hepatitis C virus infection in a United States population. Clin Gastroenterol Hepatol **2006**; 4:1278–82.
9. Martin-Carbonero L, Nuñez M, Mariño A, et al. Undetectable hepatitis C virus RNA at week 4 as predictor of sustained virological response in HIV patients with chronic hepatitis C. AIDS **2008**; 22:15–21.
10. Maheshwari A, Ray S, Thuluvath PJ. Acute hepatitis C. Lancet **2008**; 372:321–32.
11. Cox AL, Mosbruger T, Lauer GM, Pardoll D, Thomas DL, Ray SC. Comprehensive analyses of $CD8^+$ T cell responses during longitudinal study of acute human hepatitis C. Hepatology **2005**; 42:104–12.
12. Rahman F, Heller T, Sobao Y, et al. Effects of antiviral therapy on the cellular immune response in acute hepatitis C. Hepatology **2004**; 40: 87–97.
13. Sumpter R, Loo Y, Foy E, et al. Regulating intracellular antiviral defense and permissiveness to hepatitis C virus RNA replication through a cellular RNA helicase, RIG-I. J Virol **2005**; 79:2689–99.
14. Meylan E, Curran J, Hofmann K, et al. Cardif is an adaptor protein in the RIG-I antiviral pathway and is targeted by hepatitis C virus. Nature **2005**; 437:1167–72.
15. Shire NJ, Horn PS, Rouster SD, et al. HCV kinetics, quasispecies, and clearance in treated HCV-infected and HCV/HIV-1–coinfected patients with hemophilia. Hepatology **2006**; 44:1146–57.
16. McGovern BH, Abu Dayyeh BK, Chung RT. Avoiding therapeutic pitfalls: the rational use of specifically targeted agents against hepatitis C infection. Hepatology **2008**; 48:1700–12.