Acute Hepatitis C Virus Infection: A Chronic Problem

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Since the discovery of the hepatitis C virus (HCV) in the late 1980s, there has been an explosion of information regarding its natural history, treatment, and replication cycle. Nonetheless, there are still relatively few data regarding acute HCV infection. By convention, the term *acute hepatitis* refers to the presence of clinical signs or symptoms of hepatitis for a period of 6 months or fewer after the presumed time of HCV exposure. Early studies of posttransfusion patients who developed non-A, non-B hepatitis provide a clinical picture of early infection.[1] Following the availability of specific serologic and virologic tests, most such patients were shown to have acute HCV infection. After acute infection, HCV RNA may become detectable in the serum/plasma in as little as 2 weeks (Fig. 1). Several weeks later, a high percentage of patients experience an increase in serum aminotransferase levels consistent with the development of acute hepatocellular injury. In the majority of cases, patients develop mild constitutional symptoms, including abdominal pain, nausea, vomiting, anorexia, and fatigue. During this acute infection, serum aminotransferases often peak below 1000 IU/mL and may return to normal levels. A minority develops sufficient elevations in bilirubin to lead to overt jaundice or the development of dark urine. Unless the clinical suspicion is high, few patients will be tested for HCV RNA or HCV antibody seroconversion. However, in the majority—but not all—of infected patients, HCV RNA persists, and a chronic disease state develops.

The reasons for the general lack of data regarding acute HCV infection are multifactorial and include (1) the relatively high percentage of asymptomatic or unrecognized early infections, (2) the lack of large-scale identification of chronic carriers in the general population who serve as a reservoir for infection, and (3) the decreased number of acute infections that occur in controlled clinical settings such as that of blood transfusions. These factors and the lack of nonprimate animal models necessitate reliance on retrospective studies in chronic carriers, the use of limited historical collections of banked sera, and the extrapolation of outcomes based on small disease outbreaks in unique settings (for example, transmission from a physician to a patient in the operating room setting or following parenteral exposure in healthcare workers). Moreover, there exist only a limited number of population cohorts that continue to experience high rates of HCV transmission (for example, Egypt); nonetheless, there is a growing body of information regarding the clinical presentation, natural history, and treatment outcomes of acute HCV infection.

In this article, we review the current information regarding our understanding of the epidemiology, virology, and immunology of HCV with a particular emphasis on acute HCV infection. In addition, we review recent data related to interferon-based treatment intervention and propose an algorithm for the diagnosis and management of acute HCV infection.

Epidemiology and Natural History of HCV Infection

Data from the National Health and Nutrition Examination Survey estimated that more than 4.1 million people have evidence of HCV exposure, as measured by HCV antibody, in the United States.[2] This number may be even higher when homeless and incarcerated persons are taken into account, as infection rates in these populations may exceed 40%[3-6] and even 70% among human immunodeficiency virus–positive (HIV^+) urban poor.[7] Overall, approximately 85% of those with an acute infection will develop chronic disease,[8] persistent viremia occurring at least 6 months after initial exposure, with estimates ranging from 55% in the Irish anti-D immune globulin cohort[9] and 60% in a study of community-acquired HCV in the United States[10] to 90% in a single-source outbreak from contaminated clotting factors in Austria.[11] Fortunately, HCV incidence has dropped nearly 10-fold in the United States since the 1980s,[12] largely because of improved screening of blood products, decreased injection

Abbreviations: Ab, antibody; ALT, alanine aminotransferase; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HVR, hypervariable region; IDU, injection drug use; ISC, interferon secreting cell; MSM, men who have sex with men; NK, natural killer; PCR, polymerase chain reaction; PD-1, programmed death 1; PEG-IFN, pegylated interferon; PY, person years; RBV, ribavirin; SVR, sustained viral response.

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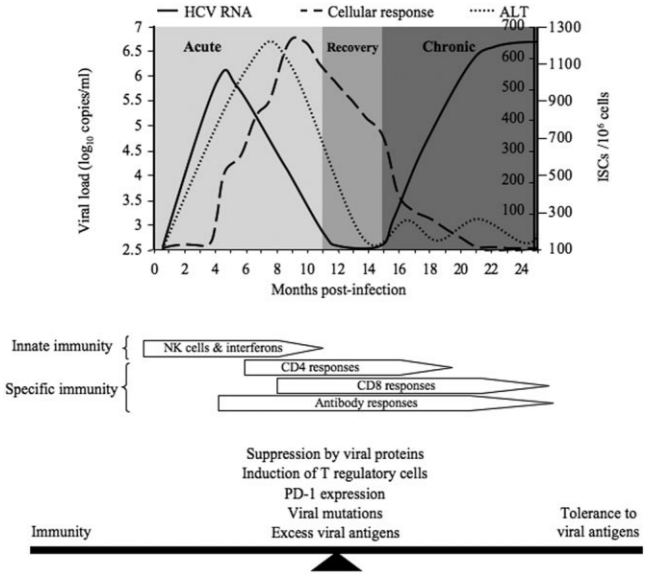

Fig. 1. Natural history of HCV infection (upper panel) and immunologic responses to HCV infection (lower panel): (–) HCV RNA, (- - -) cellular response, and (· · ·) ALT. ALT indicates alanine aminotransferase; HCV, hepatitis C virus; ISC, interferon secreting cell; NK, natural killer; and PD-1, programmed death 1.

drug use (IDU), and safer sexual practices. However, HCV still poses a significant public health threat, as most patients with an acute infection do not exhibit symptoms and therefore are unaware that they are infected and remain capable of transmitting the virus to others.

Transmission of Acute HCV Infection

It is believed that HCV can be acquired or transmitted via any blood-borne route. High-risk settings include IDU and the transfusion of unscreened blood and blood products. Other possible but less well characterized risk exposures include tattoos and piercings, needle sticks, and unsafe/traumatic sexual practices. Historically, sexual transmission has been considered a relatively inefficient route for HCV transmission. For instance, in a recent study of sexual transmission among monogamous couples in Italy, only 3 persons contracted HCV among 770 partners of persons with a chronic HCV infection who were observed during a 10-year period.[13] Another cross-sectional analysis detected a 2.5% risk of spousal HCV transmission.[14]

Despite the relatively small risk of sexual transmission of HCV, coinfection with HIV may potentially increase this risk. For instance, the Swiss HIV Cohort Study calculated an HCV incidence rate of 6.4 per 1000 person years (PY) among HIV$^+$ subjects who were HCV-seronegative at the baseline.[15] In contrast, the national rate in Switzerland is 0-4 cases per 100,000 PY. Factors increasing the risk of acute HCV infection included a history of IDU and unsafe sex. However, the association between unsafe sex and HCV seroconversion was not statistically significant in those with HIV transmission from heterosexual sex but was only among men who have sex with men (MSM). In a related study of acute HCV among HIV$^+$ MSM, 29 cases were detected in a 3.5-year study period.[16] All patients reported unprotected anal sex, whereas 6 described sexual practices with mucosal trauma. Forty-one percent had concomitant sexually transmitted diseases, although none reported IDU. Another study detected incident HCV infection in 11 of 308 HIV$^+$ MSM during a 5-year follow-up.[17] A detailed behavioral questionnaire revealed that fisting was the only significant predictor of acute HCV infection. Furthermore, an analysis of the HIV$^+$ French PRIMO Cohort followed 379 subjects without HCV at the baseline for at least 18 months. Six subjects seroconverted, yielding an HCV incidence rate of 4.3 per 1000 PY.[18] Four were male, and all reported high-risk, unprotected anal sex. Another analysis reported a statistically significant trend toward increasing HCV seroconversion, from 0.2 per 1000 PY in 1997 to 4.5 per 1000 PY in 2002 in HIV$^+$ MSM in the United Kingdom.[19] This trend was exaggerated (from 0.6-9.3 per 1000 PY) in those who received an HCV test because of elevated liver enzymes.

Collectively, these data suggest that HIV could mediate the risk of HCV transmission, particularly among MSM. There is mechanistic plausibility to support this hypothesis as well. For example, HCV viral loads are significantly elevated among individuals coinfected with HIV,[20-22] whereas the viral half-life may also be prolonged.[23] Furthermore, HCV RNA has been detected at higher rates in the semen from HIV/HCV-coinfected men[24] versus HCV-monoinfected men.[25] The practices of unprotected and traumatic anal sex increase the chance of semen-to-blood or blood-to-blood transmission, whereas concomitant sexually transmitted infections may further facilitate this process. These explanations may also help explain why similar effects of HIV on HCV transmission and acquisition are not generally observed in females.[26]

Natural History of Acute HCV

Most patients with newly acquired HCV do not exhibit symptoms of infection within the first 6 months. A prospective evaluation of 179 HCV antibody–negative injection drug users identified 62 seroconverters, yielding an incidence rate of 27.2 cases per 100 PY.[27] Of the 40 cases with available follow-up data, 8 cleared the infection. None of the patients exhibited any clinical symptoms that would warrant medical attention. Symptomatic patients may exhibit jaundice but more often will com-

plain of fatigue, nausea, abdominal pain, or flulike symptoms. In a study with a surprisingly high rate of symptoms (68%), Santantonio et al.[28] noted jaundice in 57% and alanine aminotransferase (ALT) levels greater than 20 times the upper limit of normal in 73%.[28] Seventy-three of the 203 subjects (36%) had spontaneous viral clearance—80% within 3 months of disease onset. Although symptomatic infection was not associated with clearance in this study, it has nonetheless been postulated that symptomatic patients have a higher rate of spontaneous clearance than asymptomatic patients. For instance, Gerlach et al.[29] observed a spontaneous clearance rate of 52% (24 of 46) in symptomatic acute HCV–infected patients with HIV, but clearance was not evident in any asymptomatic patients in that study. Likewise, a retrospective analysis from a non-HIV clinic population reported symptoms in 26 of 28 acute HCV cases.[30] The authors observed spontaneous clearance in 25% (7 of 28) of subjects, all of whom were symptomatic. Interestingly, this study included 4 patients, each with 2 distinct instances of acute HCV; each infection was symptomatic, and each was cleared. However, in another small study of 9 HIV^+ men with acute HCV, of whom 7 were symptomatic, 2 had spontaneous clearance, 3 responded to interferon-based treatment, and 4 developed a chronic infection.[31] Similarly, among incarcerated injection drug users, McGovern and colleagues[32] detected 21 cases of acute HCV infection. Of 17 individuals observed for more than 6 months, 8 spontaneously cleared the virus (6 of 13 patients with symptoms and 2 of 4 patients without symptoms). One patient had *de novo* HCV reinfection through IDU after spontaneous clearance and normalization of the liver enzyme, as demonstrated by sequence analysis. Although the initial infection caused jaundice, the patient remained asymptomatic during the second infection, and this was consistent with the increased likelihood of spontaneous clearance during symptomatic acute infection.

Several studies have shown that a wide spectrum of clinical, virologic, and immunologic outcomes may be exhibited after exposure, even during common source outbreaks.[9,33,34] This suggests complex interactions among various factors that result in self-limiting acute infection versus chronic infection (Table 1).

Table 1. Factors Potentially Associated with the Clearance or Persistence of an Acute HCV Infection

Type of exposure
Size of inoculum/HCV viral load
Gender
Age
Prior HCV exposure
Prior exposure to interferon therapy
HCV genotype
Quasispecies diversity/complexity
Other coinfections
Immunologic response
Innate immune response: viral evasion
Neutralizing antibody response: viral epitope recognition or escape
$CD8^+$ cytotoxic T lymphocyte response: viral epitope recognition or escape

HCV Diversity

Hepatitis C viral replication is extremely robust, producing an estimated 10 trillion viral particles per day.[35] A hallmark of RNA viruses is their extreme genetic diversity. The nonstructural 5B protein of HCV is an RNA-dependent RNA polymerase that lacks a proofreading mechanism. Thus, mutations within the HCV genome are generated at a rate of approximately 1 mutation per genome per replication cycle. This results in a population of distinct but closely related viral variants, termed the *viral quasispecies*, that exist within a single individual.

Given the diverse nature of HCV, it has been suggested that the emergence of particular viral variants may permit HCV to circumvent the host immune response and maintain persistent infection.[36-40] Moreover, several studies have explored potential associations between immunologic selection pressure and clinical outcome *in vivo*. For instance, Ray et al.[38] investigated viral diversity in 5 individuals who spontaneously cleared viremia and 10 individuals with persistent viremia. Persistent viremia was associated with a higher hypervariable region 1 (HVR1) nonsynonymous/synonymous rate ratio, a lower E1 nonsynonymous/synonymous rate ratio, higher quasispecies complexity, and fewer positively charged residues in HVR1. Spontaneous clearers also differed from individuals with persistent viremia at 8 amino acid positions, although no residues were completely predictive of clinical outcome. Farci et al.[39] similarly examined viral diversity among 12 patients with different clinical outcomes. Acute resolving hepatitis was associated with relative stasis of the viral quasispecies, whereas progressing hepatitis correlated with HCV evolution, particularly in HVR1.

Innate Immunity to HCV Infection

An acute viral infection triggers the activation of several antiviral effectors in mammalian cells. This innate antiviral response is an early host defense mechanism that occurs prior to adaptive immune responses.[41] The recent discovery of pathogen-associated molecular patterns that are recognized by specific toll-like receptors have dramatically advanced our understanding of the innate host response to viral infection.[42] For example, HCV RNA contains pathogen-associated molecular pattern motifs[43,44] that could bind to toll-like receptor 3 at the cell

surface and intracellularly through retinoic acid–inducible gene 1 to induce type I interferons (interferon alpha and interferon beta) in hepatocytes.[43,45] Type I interferons regulate the antigen-processing machinery through the induction of immunoproteasome subunits, their incorporation into the proteasome complex, and the generation of an immunoproteasome-dependent CD8 T cell epitope.[46] Moreover, type I interferons activate the expression of more than 300 interferon-stimulated genes that also have antiviral functions. The best characterized include the RNA-dependent protein kinase (PKR), 2′5′-oligoadenylate synthetase, RNase L, adenosine deaminase (adenosine deaminase, RNA-specific), and the Mx protein GTPases.

It is generally thought that only a minority of hepatocytes are infected with HCV.[47] Nonetheless, the gene products secreted by this small number of infected cells can produce a transient antiviral state in neighboring uninfected cells. Although such a scenario would limit the potential replicative space within the liver, it is rare that this innate antiviral response completely eradicates the virus as the majority of persons exposed to HCV develop a chronic infection. Thus, the ability of HCV to antagonize these antiviral responses is crucial to viral persistence. Several HCV proteins, including core, E2, nonstructural 3/4A, and nonstructural 5A proteins, have been implicated in the inhibition of interferon-inducible genes and/or key components of interferon signaling pathways via multiple mechanisms.[48] Thus, HCV can both trigger and control the hepatic response to infection (Fig. 1).

Role of Natural Killer (NK) Cells

NK cells are the major effector cells of the innate immune system and play an important role in the activation and maintenance of subsequent adaptive immune responses. The antiviral role of NK cells during HCV infection has been demonstrated by the induction of an HCV-associated, perforin/granzyme-dependent lysis of human hepatoma cells by cytokine-activated NK cells.[49] The ligation of CD81 (a potential receptor for HCV) on NK cells inhibits interferon gamma production and results in decreased anti-HCV activity. In addition, antibodies to interferon gamma or interferon gamma receptors abolish the anti-HCV activity of NK cells.[50] Furthermore, genes encoding an inhibitory NK cell receptor (killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 3) and its human leukocyte antigen C group 1 ligand directly influence the resolution of HCV infection,[51] and this suggests that inhibitory NK cell interactions are important determinants of antiviral immunity and that diminished inhibitory responses confer protection against HCV.

Humoral Immune Responses

Humoral immune responses are generated against multiple HCV proteins, but the correlation of a single specific immune response with recovery from an acute infection has not been clearly established. Two HVRs (HVR1 and HVR2) in the E2 envelope glycoprotein have been identified.[52,53] At least 1 study has suggested that the early appearance of HVR1 antibodies is associated with an acute self-limiting HCV infection.[54] Additionally, mutations within certain regions, especially the E2 HVR, have been associated with the emergence of virus resistance to neutralization and the persistence of infection.[55] Recently, discordance between the level of neutralizing anti-HCV antibodies and clearance of viremia has been reported.[56] In fact, there exists a subpopulation of individuals exposed to HCV that clear the virus without the induction of anti-HCV antibodies; therefore, the only surrogate markers for HCV exposure in such persons are HCV-specific cell-mediated immune responses.[57-63]

Role of CD4 T Cells

A growing body of evidence indicates that the spontaneous clearance of HCV is associated with a strong HCV-specific $CD4^+$ T cell response.[56,64,65] A number of studies have indicated that successful cellular immune responses in recovered patients appear to be multispecific and sustained, with $CD4^+$ T cells playing major roles.[66-73] The role of $CD4^+$ T cells in acute HCV infection has been examined by depletion studies in chimpanzees, in which the loss of $CD4^+$ T cells resulted in persistent infection.[74] $CD4^+$ T cell levels also appear to be important during acute HCV infection, as the level of $CD4^+$ T cell proliferative responses is associated with viral clearance,[65,75,76] whereas the loss of such responses often results in the recurrence of viremia.[77] Moreover, it has also been shown that patients who clear the infection respond to higher numbers of HCV epitopes in comparison with chronically infected patients.[66,78]

Cytokines are also important for the clearance or persistence of viremia. For instance, a vigorous HCV-specific type 1 helper T cell $CD4^+$ response, particularly against nonstructural proteins, is associated with viral clearance[65] or a successful response to therapy.[76,79-82] In fact, the lack of type 1 helper T effector cells within the first months of acute HCV is a predictor of viral persistence and could thus serve as a criterion for selecting candidates for early antiviral treatment.[65] The cause of dysfunctional $CD4^+$ T cells in chronic HCV infection is not clear. However, exhaustion from continuous T cell stimulation,[83] the induction of T-cell anergy,[84] the induction of T regulatory cells that inhibit the immune responses,[85,86] and the sup-

pression of immune responses by HCV proteins[48,87-93] represent several intriguing hypotheses. Without sufficient HCV-specific CD4 help, HCV-specific $CD8^+$ T cell and heterologous neutralizing antibody responses may develop but fail to clear viremia.[56]

Role of CD8 T Cells

CD8 T cells could respond to HCV viral infection through 2 main mechanisms: the killing of infected hepatocytes or the secretion of antiviral cytokines. In comparison with $CD4^+$ T cells, the role of $CD8^+$ T cells in an acute HCV infection is less well defined because their detection during an acute infection coincides with viral clearance in some[94,95] but not all studies.[96] The reason for this discrepancy is not clear; however, most studies have used peripheral blood lymphocytes stimulated with selected epitopes previously identified or predicted from protein sequences. Therefore, this approach may not adequately evaluate the local intrahepatic immune responses to naturally processed HCV peptides. A comprehensive analysis of the CD8 responses using overlapping peptides covering the entire HCV genome has revealed multiple unpredicted epitopes that stimulate CD8-specific T cells even in chronically HCV-infected patients.[97] Moreover, differences also exist between intrahepatic T cell responses and those in the peripheral blood.[98-100] However, strong, multispecific interferon gamma–producing, HCV-specific $CD8^+$ T cells are one of the characteristic features of patients who recover from an acute HCV infection.[66,68,69,72,101-114] In a chronic HCV infection, although the frequencies of HCV-specific $CD8^+$ T cells may be normal, the cells exhibit a dysfunctional or stunned phenotype.[66,100,115,116] Recent data indicate that most HCV-specific $CD8^+$ T cells express the inhibitory receptor programmed death 1 (PD-1) at the time of acute infection.[117] Interestingly, levels of PD-1 decline in patients with a resolved HCV infection but remain high during viral persistence.[117] The high expression of PD-1 is associated with dysfunctional $CD8^+$ T cells and may partially explain the defective phenotypes of $CD8^+$ T cells reported in chronically HCV-infected patients. Blocking the PD-1/programmed death ligand 1 interaction improved the functional activity of HCV-specific $CD8^+$ T cells and restored CD8 function *in vitro*.[118] Supporting data for the role of PD-1 expression in chronic HCV infection has been recently published with chimpanzees models.[119] However, there are also data suggesting that most intrahepatic $CD8^+$ T cells are toleragenic and express PD-1.[120] One of the evasion mechanisms used by HCV to escape immune responses, especially CD8 responses, is the development of viral escape mutants.[121] Finally, a significant correlation has been demonstrated between the number of lobular $CD8^+$ T cells and ALT levels, suggesting a prominent role for T cell–mediated cytotoxicity in the genesis of hepatocellular damage.[122]

Treatment of Acute HCV Infection

Treatment decisions related to acute HCV infection must be considered in light of the natural history of the disease process. Although early treatment may increase the likelihood of improved treatment outcome, this must be balanced against the possibility that spontaneous clearance during the acute phase of infection could render treatment interventions needless and potentially harmful. Therefore, treatment paradigms must effectively balance these outcomes and lead to optimal patient selection without significant loss of treatment efficacy.

As in chronic infection, all current acute HCV treatment paradigms are interferon-based. Mechanistically, issues related to both viral evolution and immune response must be considered in the context of interferon use. Several studies now suggest that quasispecies diversity is an independent predictor of HCV treatment response. For instance, Chambers et al.[123] noted that an early treatment response to pegylated interferon alpha 2a and ribavirin (RBV) was associated with lower baseline HCV RNA complexity in the envelope coding region, although this was not the exclusive predictor of sustained viral response (SVR). Among subjects with advanced liver disease, the treatment response was also reduced in subjects with increased baseline quasispecies complexity.[124] Shire et al.[125] examined the relationship between baseline and early viral selection pressures in HCV-monoinfected and HIV/HCV-coinfected subjects with hemophilia who were treated with pegylated interferon plus weight-based RBV. Lower baseline quasispecies complexity was associated with SVR. At the end of the phase 1 decline in HCV viremia, subjects whose decrease was greater than 90% also had a strong trend toward lower baseline complexity. The presence of HIV coinfection further mediated changes in the complexity over time. Thus, low pretreatment quasispecies complexity may predict the pegylated interferon response. These data do not, however, permit the ascertainment of the latest time following acute exposure at which HCV infection can be treated with maximum effect.

Multiple clinical trials report the arbitrary selection of start times for treatment intervention after the recognition of HCV infection. However, because of the variability among treatment regimens, current clinical recommendations are derived from diverse population cohorts with data extrapolated to individual patients. Jaeckel et al.[126] described the treatment response among 44 German patients with acute HCV. Patients had known or

suspected exposure within 4 months, as documented by HCV seroconversion or a serum ALT greater than 20 times the upper limit of normal with evidence of previously normal ALT for 1 year. Patients were treated with interferon alpha 2b at a dose of 5 MU per day for 4 weeks followed by 5 MU 3 times per week for 20 weeks. Sixty-eight percent met the first entry criteria for documented seroconversion; 61% were infected with HCV genotype 1. Fully 98% of the subjects achieved SVR. Subsequently, another German study evaluated a 24-week course of pegylated interferon alpha 2b.[127] The overall SVR was 71%, although an 89% SVR rate was achieved among subjects classified as adherent with prescribed therapy. A third German experience by Gerlach et al.[29] included 60 patients with acute HCV by either seroconversion or acute hepatitis with ALT greater than 10 times the upper limit of normal. There was no randomization or fixed time for treatment intervention, and patients were offered the most effective therapy at the time of diagnosis. Fifty-two percent spontaneously cleared HCV RNA less than 12 weeks after diagnosis. Only 26 subjects were treated with an interferon-based regimen; 12 had therapy started more than 6 months after the diagnosis of acute HCV. Twenty received pegylated interferon, and half of those had coadministration of RBV. Viral clearance was observed in 21 of 26 (81%) treated subjects, leading to SVR. Kamal et al.[81] described 54 patients screened after either the first positive HCV RNA or the onset of symptoms. Laboratory studies were performed for 12 weeks, and then HCV RNA–positive subjects were offered interferon-based therapy [either pegylated interferon alpha 2a (180 μg/week) $\pm$ RBV (800 mg/day) or pegylated interferon alpha 2b (1.5 μg/kg/week) $\pm$ weight-based RBV]. Only 4 subjects cleared the virus during the 12-week period without treatment. Ten subjects refused therapy, and 1 of these cleared at week 14. All subjects had either genotype 1 or 4, with a slight genotype 4 predominance. Among the treated subjects, 33 of 40 (82.5%) achieved SVR. There was a nonstatistically significant advantage to subjects treated with regimens containing RBV. Subsequently, Kamal et al. evaluated the optimization of the treatment duration and time of initiation in 2 randomized treatment trials. Among 102 subjects randomized to receive pegylated interferon alpha 2b for 8, 12, or 24 weeks, the highest rate of response was observed in the 24-week arm (91.2%). Although stratification by genotype led to relatively small subsets (only 15-16 subjects per arm), 88% of genotype 1 subjects who were treated for 24 weeks achieved SVR. Excellent results were reported for shorter therapy in genotype 2 and 3 subjects; however, each treatment arm contained only 2 or 3 subjects, and this limited interpretation. Genotype 4 was nearly as common as genotype 1 and had the highest response (100% SVR) in the 24-week treatment group.[128] In a second study, Kamal et al.[129] followed patients for 8 weeks after the identification of acute HCV. Subjects were then randomized to receive pegylated interferon alpha 2b, beginning at 8, 12, or 20 weeks, and they underwent a 12-week treatment regimen. SVR was higher for subjects with shorter waiting times.

Reports of acute HCV within the United States are limited. The largest experience involves a retrospective analysis of clinical practices reported by Corey et al.[30] Acute HCV was diagnosed in 24 patients; 15 received interferon-based therapy. All treated patients cleared the virus on therapy, and all but 1 (93%) achieved SVR; 5 of 6 patients not offered therapy remained viremic. A similar study by Rahman et al.[130] included 7 patients who were treated with an interferon-based regimen; 6 of 7 achieved SVR. Interestingly, the only patient to not achieve SVR did not receive RBV; however, the authors noted that this patient was also an African American male with poor prognostic likelihood of viral clearance, obscuring potential conclusions regarding the cause of treatment failure.

As mentioned previously, patients with acute HCV infection in the setting of HIV coinfection represent a unique and increasingly important subset of this disease process.[19] A prospective evaluation for liver function test abnormalities and HCV antibody seroconversion was performed every 3 months in an HIV clinic in Great Britain. Fifty acute HCV infections were identified and confirmed with HCV RNA testing, and this was followed every 4 weeks with HCV RNA quantitative assays. After 12 weeks of positive HCV RNAs, patients were offered therapy with pegylated interferon and weight-based RBV. During the 12-week window, 12 of 50 (24%) cleared HCV RNA and remained aviremic. Eleven subjects declined therapy, and all progressed to chronic HCV infection. The remaining 25 were treated for 24 weeks. SVR was 59% among the treated patients, and this is clearly lower than reports during HCV monoinfection. All treatment failures occurred among patients with HCV genotype 1 and relatively low CD4 counts (median: 276 cells/mm^3). However, better response rates were reported among 11 acutely infected German patients, with 10 having SVR.[131] Ten patients with genotype 4 HCV and HIV were treated in France following a suspected common source sexually transmitted infection cluster. Treatment was provided within a mean time of 49 days from the onset of acute hepatitis, and a variety of interferon-based regimens were used. No patient achieved SVR.[132] Finally, 9 acute HCV infections were identified in HIV-infected patients in California.[31] Only 4 were treated with pegylated interferon and RBV; 3 achieved SVR. Among 5

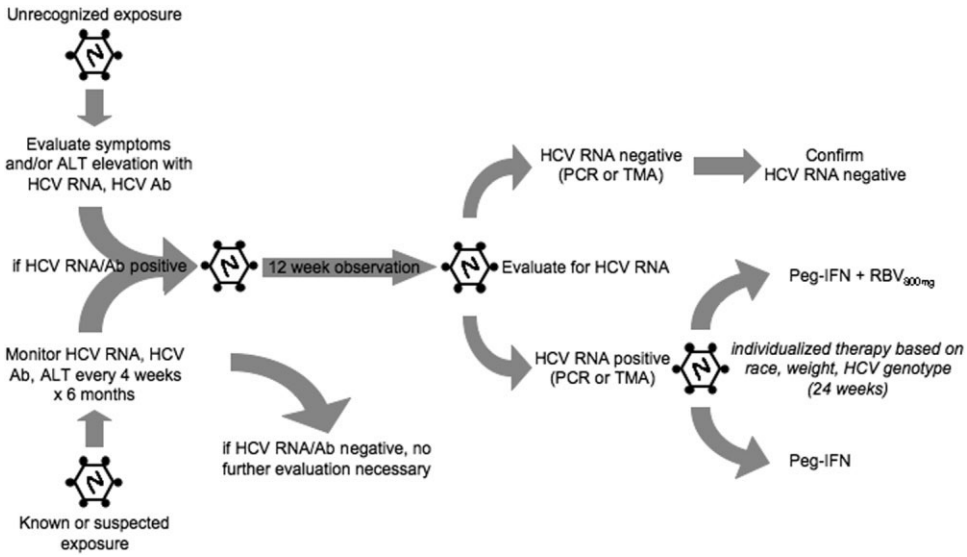

Fig. 2. Proposed algorithm for the diagnosis and treatment of an acute HCV infection. Ab indicates antibody; ALT, alanine aminotransferase; HCV, hepatitis C virus; PCR, polymerase chain reaction; PEG-IFN, pegylated interferon; and RBV, ribavirin.

untreated patients, 2 demonstrated spontaneous clearance, and 3 developed chronic liver disease.

On the basis of the available (albeit insufficient) data, several conclusions may be drawn. First, the optimal timing to initiate treatment remains unclear. Different definitions of decision trees used in clinical trials contribute to some of this confusion because some studies define the estimated time from acute exposure, whereas others define the starting point as seroconversion or acute hepatitis, using arbitrary serum aminotransferase criteria. The only study to prospectively evaluate this issue used 12 weeks of therapy, although the same group reported better efficacy with 24 weeks of therapy in another cohort. These inconsistencies argue for a formal definition to be used in future prospective trials (Fig. 2). Although the first HCV RNA–positive result may be useful, in unsuspected, community-acquired cases, clinical findings are often used to reach an eventual diagnosis. It is reasonable to suggest that treatment should be considered at least 12 weeks after seroconversion or acute hepatitis. In the future, increased availability of more sensitive HCV assays (for example, transcription-mediated amplification) may require reassessment of this algorithm because of the potential for earlier diagnosis. The latest time at which the treatment of acute infection may be initiated has not been precisely defined; however, the data support the concept that earlier treatment may be more effective than later treatment. Although excellent responses have been observed with standard interferon, clinical experience suggests that the use of once weekly agents improves adherence and is preferred.[133] Therefore, pegylated interferon use is recommended. Second, the need for RBV with an interferon-based treatment remains controversial. European experts suggest that RBV use is unnecessary on the basis of excellent response rates observed with monotherapy.[63] However, response rates have not been as high in the United States. The extrapolation of data from the treatment of chronically HCV-infected patients would support RBV use in the United States. Pending further data, a dose of 800 mg of RBV per day combined with pegylated interferon seems ideal, although patients with poor response characteristics may require weight-based dosing regimens. Treatment durations of 24 weeks have been shown to be more effective in genotype 1 patients in 1 prospective trial; therefore, this treatment cycle should be used in HCV-monoinfected patients because excellent overall responses have been observed. These recommendations are similar to those promulgated by the American Association for the Study of Liver Diseases,[134] although that body felt that RBV use should be individualized. Finally, patients with HIV/HCV coinfection seem to have poorer outcomes following acute HCV infection. At this time, there are no data to support either longer treatment durations or higher doses of interferon products, and no specific recommendations can be made.

Conclusions

Acute HCV infection remains a significant clinical problem because of the difficulty of early case recognition and the inability to predict the risk of clearance versus chronicity of infection with a high degree of accuracy during early infection. Research focused on either virologic or immunologic events that signal spontaneous clearance should be vigorously pursued. Similarly, a lack of large, randomized clinical trials limits our ability to make informed treatment decisions and leads to the development of treatment paradigms that are often vigor-

ously defended by their proponents yet poorly supported by the data available. Studies of timing, duration, and dose are needed. However, these studies are difficult to perform, and investment is often tempered by the rapid evolution of agents used in more common chronic infection scenarios. Therefore, it seems likely that existing regimens will dominate the acute HCV scene for several years to come.

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