

Review

## Acute hepatitis C: Current status and remaining challenges<sup>☆</sup>

Teresa Santantonio<sup>1,\*</sup>, Johannes Wiegand<sup>2,3</sup>, J. Tilman Gerlach<sup>4,5</sup>

<sup>1</sup>*Clinic of Infectious Diseases, University of Bari, Policlinico, Piazza G. Cesare 11, 70124 Bari, Italy*

<sup>2</sup>*Department of Internal Medicine II, University of Leipzig, Philipp-Rosenthal-Strasse 27, 04103 Leipzig, Germany*

<sup>3</sup>*Department of Gastroenterology, Hepatology, and Endocrinology, Hannover Medical School, Hannover, Germany*

<sup>4</sup>*Department of Gastroenterology and Hepatology, University of Zurich, Rämistrasse 100, 8091 Zurich, Switzerland*

<sup>5</sup>*Department of Gastroenterology and Hepatology, Kantonsspital St. Gallen, Rorschacherstrasse 95, 9007 St. Gallen, Switzerland*

The acute phase of hepatitis C virus (HCV) infection represents a key point in the evolution of hepatitis C. In some patients, the infection resolves spontaneously, whereas in others it develops into chronic disease. However, because acute hepatitis C is often asymptomatic, detection and diagnosis are usually difficult. What is more, there are no established treatment guidelines, leaving physicians to make several challenging decisions, such as whether to treat, when to treat and what treatment regimen to use. Pegylated interferon alfa monotherapy is most commonly used to treat patients with acute hepatitis C; the role of ribavirin has yet to be established. In this review, we discuss the epidemiology of acute hepatitis C, its risk factors and routes of transmission and current treatment practices. We also discuss data from published clinical studies and focus on unresolved issues for which additional studies are needed in order to establish standardized treatment guidelines for the management of acute hepatitis C.

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### 1. Introduction

In the past decade, the introduction of pegylated interferons (PEG-IFNs) and the identification of host and viral factors that can predict sustained virological response (SVR) have improved the treatment of chronic hepatitis C. In contrast, because of the lack of a diagnostic marker for acute hepatitis C virus (HCV) infection and its relatively silent nature, prospective clinical investigations of acute hepatitis C have been difficult to conduct. In this review, we attempt to synthesize existing information on acute hepatitis C to provide a comprehensive overview of this condition, describe the natural

history and epidemiology of the disease and discuss the best treatment practices.

### 2. Epidemiology

Patients with acute HCV infection are generally asymptomatic, which renders diagnosis difficult and results in under-reporting [1,2]. Identification of patients with acute hepatitis C is also hindered because many patients are reluctant to divulge habits that may lead to infection. As a result, estimates of the incidence vary widely and are probably lower than the real figure. For example, in Italy, incidence estimates range from 1 to 14 cases per 100,000, according to whether the population evaluated included patients with acute HCV reported to the National Surveillance Agency [3], Italian blood donors, [4] or the general population [5]. In the United States, the incidence of acute hepatitis C has declined in recent years [6–8], with the Department of Health and Human Services Center for Disease Control and

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\* Corresponding author. Tel.: +390805478237; fax: +390805478333.

E-mail address: t.santantonio@clininf.uniba.it (T. Santantonio).

† Address: Internal Medicine, Immunology and Infectious Diseases, Piazza G. Cesare 11, Bari 70124, Italy.

Prevention reporting 671 acute hepatitis C cases in 2005 for an overall national rate of 0.2 per 100,000. However, after accounting for under-reporting of asymptomatic infections, the estimated total was 20,000 new infections [9].

### 3. Risk factors, routes of transmission and diagnosis

Currently, intravenous drug use, unprotected sex with multiple partners, and viral exposure during medical procedures, such as surgery, dialysis and dental treatment, are factors associated with the highest degree of risk for HCV infection [9–13]. Health care employees are at risk for acute hepatitis C through accidental exposure, such as needlestick injury; however, recent reports indicate that the risk for HCV transmission after needlestick injury is lower than that previously believed (mean value 0.75%; in Europe 0.42%; in Eastern Asia 1.5%) [14]. Of note, risk factor patterns vary according to geography. For example, within many Western countries intravenous drug use is the greatest risk factor, with sexual transmission and medical practices representing other less common risk factors [10,11,15]. Conversely, in Egypt, occupational exposure seems to be the greatest hazard, with intravenous drug use and sexual transmission less evident [16,17]. Although guidelines exist for

the management of chronic hepatitis C [18,19], they do not specifically address *acute* hepatitis C. Table 1 summarizes recommendations for persons who are at risk and should be tested for HCV infection.

After exposure to HCV, there is a window of 1–3 weeks before serum HCV RNA can be detected. In patients in whom symptoms are developing, the incubation period between exposure and appearance of symptoms can range from 2 to 12 weeks [1]. The most common symptoms are fatigue and jaundice, with dyspepsia and abdominal pain often reported [20,21]. Given that most symptoms are non-specific, many patients do not consult a physician and do not receive a diagnosis during the acute phase. The first indication of hepatic injury is an elevated alanine aminotransferase (ALT) level, which can occur 4–12 weeks after viral exposure [22]. Fulminant liver injury is rare and occurs in less than 1% of patients.

Diagnosis of acute HCV infection is confirmed by the detection of HCV RNA with documented anti-HCV antibody seroconversion (Table 2). Seroconversion may occur 4–10 weeks after exposure to HCV [23,24]. Other criteria that can aid in diagnosing HCV infection include significantly elevated ALT levels ( $>10\times$  ULN or  $>20\times$  ULN), known or suspected exposure to HCV and increasing numbers of reactive proteins in a recombinant immunoblot assay confirmation test [23,25].

**Table 1**  
Relative risk for hepatitis C transmission and recommendations for testing

At-risk population	Recommendations for testing <sup>a</sup>
<i>High risk</i>	
Injection drug users	All persons who have injected illicit drugs in the recent or remote past, including those who have injected only once and do not consider themselves to be drug users
Blood transfusion recipients or transplantation before 1992	All patients who were notified that they received blood from a donor who later tested positive for HCV Persons who received transfused blood or blood products or transplanted organs before July 1992, including patients who received clotting factor concentrates before 1987
Hemodialysis patients	All patients with current or previous history of hemodialysis
<i>Moderate risk</i>	
High-risk sexual activity <sup>b</sup>	All sexual partners of HCV-infected patients
Vertical transmission from mother to child	All children born to mothers infected with HCV
<i>Low risk</i>	
Occupational exposure	All health care, emergency medical, and public safety workers after a needlestick injury or mucosal exposure to HCV-positive blood
Sexual activity with long-term partners <sup>b</sup>	All sexual partners of HCV-infected patients <sup>c</sup>
<i>Very low risk/no risk</i>	
Casual contact	Routine testing not required
Household contact	Routine testing not required

Table adapted from 2004 AASLD practice guidelines [18,19].

<sup>a</sup> Treatment guidelines recommend that patients suspected of having HCV infection should be tested for HCV antibodies; those with detectable HCV antibodies should undergo HCV RNA testing with use of a highly sensitive assay such as reverse transcription-polymerase chain reaction. Routine testing is recommended for patients with HIV infection and those with unexplained elevated aminotransferase levels.

<sup>b</sup> Sexual transmission of HCV is not clearly understood. However, certain high-risk sexual behaviors have been associated with HCV transmission, such as anal sex, sex with trauma, sex in the presence of a sexually transmitted disease, and sex without a condom.

<sup>c</sup> Although the prevalence of infection is low, a negative test result in the partner provides reassurance, making testing of sexual partners beneficial in clinical practice.

**Table 2**  
Proposed criteria for diagnosis of acute hepatitis C infection

Primary criteria	Presence of HCV RNA in serum of a previously HCV-negative patient. Seroconversion from anti HCV-negative to anti HCV-positive
Secondary criteria	Elevated transaminase level $\geq 10$ to 20 times the upper limit of normal Known or suspected exposure to HCV within the preceding 6 months All other causes of acute liver damage excluded
Additional considerations	Sudden onset of liver disease Repetition of recombinant immunoblot assay testing to demonstrate eventual increase in the number of reactive proteins

#### 4. Spontaneous resolution of acute hepatitis C

An average of 26% of patients with acute hepatitis C (range 20–67%) experience spontaneous clearance of the virus, an event that occurs primarily during the first 3 months after clinical onset of disease [10,11,21,26–28]. If viremia persists for more than 6 months, chronic disease should be considered. Several host and viral factors, such as HLA, HCV genotype, co-infection with human immunodeficiency virus (HIV), gender, race and advanced age seem to influence the clinical course of disease [29], but none of these parameters can accurately predict spontaneous resolution [2]. However, it seems that spontaneous resolution occurs more frequently in the presence of symptomatic disease [10,21,27,30]. Interestingly, several reports have now stated that a strong and multispecific cellular immune response is an important host factor for spontaneous viral eradication [31–38].

Follow-up testing of HCV RNA levels in patients who experience spontaneous resolution is highly recommended because a late relapse may occur after the initial HCV RNA clearance [27]; therefore, HCV RNA should be monitored for a period of at least 6 months with 2–3 consecutive tests, and subsequent testing if ALT elevation is observed. Ultimately, comparison of rates of spontaneous viral clearance across studies of acute hepatitis C natural history will be possible only with the introduction of standardized definitions and methodologies [39].

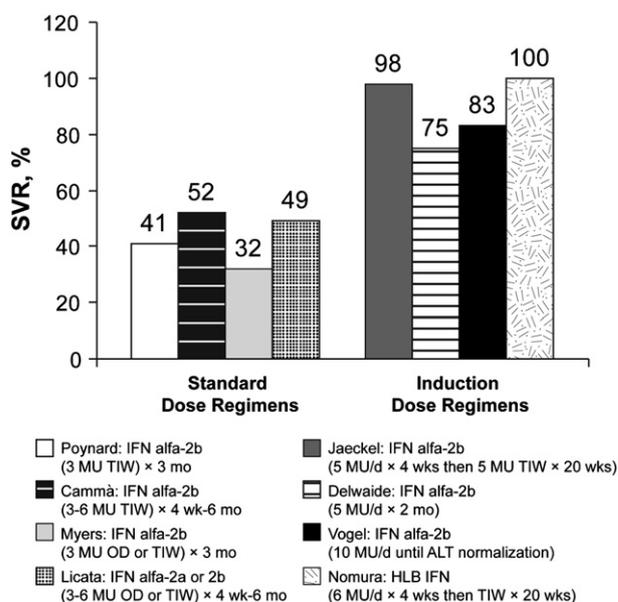
#### 5. Treatment of acute hepatitis C

Clinical trials focusing on the treatment of acute hepatitis C are hindered by the difficulties in its diagnosis. Many patients who might otherwise be candidates for treatment manifest high-risk behavior, such as ongoing intravenous drug abuse, and are thus unsuitable for clinical trials. As a result, most studies of acute hepatitis C are open-label, non-comparative investigations with

small patient populations that differ widely with respect to design, patient population and treatment regimens; therefore, discerning the most effective intervention remains difficult. The lack of comparative studies has precluded the possibility that any one treatment regimen can become a gold standard.

##### 5.1. Conventional interferon- $\alpha$

Treatment of acute hepatitis C patients with conventional (non-pegylated) interferon (IFN)  $\alpha$  has been investigated in several small clinical trials, which typically used 3–6 million units (MU) IFN  $\alpha$  administered three times weekly for 4–24 weeks. These studies examined biochemical and virological response rates, and the results have been summarized in several meta-analyses (Fig. 1). Overall, 32–52% of patients treated with IFN  $\alpha$  attained SVR (defined as undetectable HCV RNA 24 weeks after completing therapy) compared with only 4–11% of untreated patients [40–42]. The most recent meta-analysis by Licata et al. [43] showed that IFN treatment significantly increased SVR rates (risk difference, 49%; 95% CI, 32.9–65%) compared with untreated control patients. Moreover, SVR rates increased with higher weekly doses of IFN. Thus, higher IFN dosages during the first month appear to be the best treatment option. In fact, an induction regimen of IFN  $\alpha$ -2b (5 MU/day for 4 weeks, followed by 5 MU three times weekly for another 20 weeks) was shown to be highly



**Fig. 1.** Sustained virological response rates among patients with acute hepatitis C who received standard or induction doses of conventional interferon  $\alpha$ -2b (IFN  $\alpha$ -2b) [40–44,46–48]. Studies of Poynard [42], Cammà [41], and Licata [43] are meta-analyses that included at least one study of interferon- $\beta$ . Data from Licata et al. [43] include one study of induction therapy (Jaeckel et al. [44]) and represent the risk difference for attaining undetectable HCV RNA versus no treatment. ALT, alanine aminotransferase; HLB IFN, human lymphoblastoid interferon.

effective in treating patients with acute hepatitis C [44]. In this study, 43 of 44 (98%) patients attained SVR, with a mean time of 3.2 weeks from initiation of treatment to undetectable HCV RNA. Twenty-four of these patients were followed up for a median of 135 weeks; all had undetectable HCV RNA and no evidence of liver disease [45].

Other studies have evaluated the efficacy of early treatment intervention with high-dose IFN alfa and shorter treatment durations (Fig. 1). In two studies, SVR was reported in 21 of 28 (75%) patients receiving high-dose regimens of IFN alfa (5 MU/day) for 8 weeks [46] and in 20 of 24 (83%) patients treated with 10 MU IFN alfa administered daily until normalization of ALT levels [47]. In a separate study, administration of intramuscular human lymphoblastoid IFN alfa (6 MU/day) for 4 weeks resulted in SVR in 13 of 15 (87%) patients [48]. Two patients with detectable HCV RNA at the end of the treatment subsequently attained SVR when treated with IFN alfa (6 MU three times weekly) for an additional 20 weeks [48]. In addition, Nomura and colleagues also compared the response rate achieved with early initiation of treatment (8 weeks after disease

onset) with a delayed treatment strategy and demonstrated that therapy initiated after one year is clearly less effective [48]. Similarly, in the meta-analysis by Licata et al. delaying initiation of therapy until 60 days after onset of disease did not compromise the probability of a favorable response [43]. Overall, published data indicate that acute hepatitis C can be effectively managed with early or delayed treatment (8-weeks) using a 4- to 24-week course of conventional IFN alfa.

## 5.2. Pegylated interferon alfa

Treatment of chronic hepatitis C has advanced with the introduction of pegylated interferon (PEG-IFN) alfa, which, in combination with ribavirin, has become the current standard of care. Different strategies have been explored to optimize SVR rates in patients with acute hepatitis C treated with PEG-IFN alfa-2b (Table 3, Fig. 2). When considering treatment initiation, several time points have been evaluated, ranging from immediately after diagnosis to after an observation period of several weeks. In a study conducted by Wiegand et al. [15], 89 patients were treated after a median time

**Table 3**  
Treatment of acute hepatitis C with pegylated interferon alfa

Study	Study design	Treatment	Therapy duration (wk)	Time from diagnosis/infection to treatment (median)	EOT	SVR	Predictors of SVR
Wiegand et al. [15]	Open label, uncontrolled ( <i>n</i> = 89)	PEG-IFN alfa-2b (1.5 µg/kg/wk)	24	76 days	82% <sup>a</sup>	63/89 (71%) <sup>a,b</sup>	ALT >500 U/L ( <i>P</i> = 0.039)
De Rosa et al. [50]	Open label, uncontrolled ( <i>n</i> = 19)	PEG-IFN alfa-2b (1.06-1.66 µg/kg/wk)	12	31 days	NR	14/19 (74%)	PEG-IFN dose: ≥ 1.33 µg/kg/wk ( <i>P</i> = 0.0379)
Calleri et al. [52]	Open label, uncontrolled ( <i>n</i> = 46)	PEG-IFN alfa-2b (1.0-1.5 µg/kg/wk)	12	15 days <sup>c</sup>	41/46 (89%)	33/46 (72%)	PEG-IFN alfa-2b dose ≥ 1.2 µg/kg/wk ( <i>P</i> = 0.014)
Santantonio et al. [49]	Open label, uncontrolled ( <i>n</i> = 16)	PEG-IFN alfa-2b (1.5 µg/kg/wk)	24	12-week observation period	15/16 (94%)	15/16 (94%)	NR
Broers et al. [67]	Open label, uncontrolled ( <i>n</i> = 14)	PEG-IFN alfa-2b (1.5 µg/kg/wk)	24	1-50 weeks	86%	57%	Active IVDU >80% of the scheduled drug
Kamal et al. [30]	Randomised, comparative ( <i>n</i> = 40)	PEG-IFN alfa <sup>d</sup> vs PEG-IFN alfa <sup>d</sup> + RBV (800 mg/d or >10.6 mg/kg/d)	24	12-week observation period	18/20 (90%) vs 19/20 (95%)	17/20 (85%) vs 16/20 (80%)	NR
Kamal et al. [17]	Randomised comparative ( <i>n</i> = 68 <sup>e</sup> )	PEG-IFN alfa-2b (1.5 µg/kg/week)	12	8-12 weeks	30/34 (88.2%)	28/34 (82.4%)	NR
			24	8-12 weeks	32/34 (94.1%)	31/34 (91.2%)	NR

EOT, end-of-treatment response; IVDU, intravenous drug users; NR, not reported; SVR, sustained virological response.

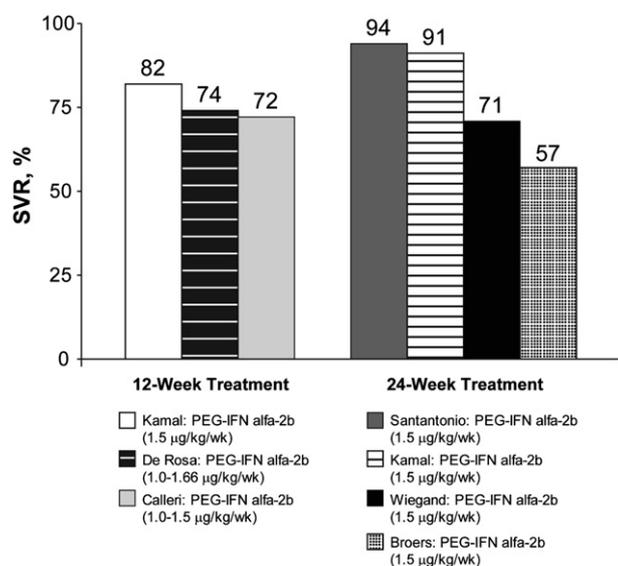
<sup>a</sup> Included patients who attained SVR while receiving PEG-IFN alfa-2b once every 2 weeks (*n* = 1) or for a shorter period of 8 to 16 weeks because of tolerability (*n* = 4).

<sup>b</sup> 70/89 (79%) patients received ≥80% of the planned dose for ≥80% of the intended duration. In these patients, the EOT response rate was 94% and the SVR rate was 89%.

<sup>c</sup> Treatment was initiated immediately after diagnosis.

<sup>d</sup> 24 subjects received PEG-IFN alfa-2a (180 µg/kg/wk) (*n* = 12 monotherapy and *n* = 12 combination therapy), and 16 patients received PEG-IFN alfa-2 b (1.5 µg/kg/wk) (*n* = 8 monotherapy and *n* = 8 combination therapy).

<sup>e</sup> Data from the 8 week treatment arm (*n* = 34) not presented.



**Fig. 2.** Sustained virological response (SVR) among patients with acute hepatitis C who received pegylated interferon alfa-2b for 12 or 24 weeks. Data from Kamal et al. [17] were derived from separate treatment arms in the same study.

from symptoms to therapy of 27 days (range 5–131) using the standard dosage for chronic HCV infection (1.5 µg/kg/wk); after 24 weeks of treatment, the overall SVR rate was 71%, but it increased to 89% in the subset of patients receiving 80% of the scheduled dosage within 80% of the planned treatment period. The difference in response rates between adherent and intent-to-treat populations was attributed to the large number of patients lost to follow-up, protocol violations, and treatment failure among the patients receiving PEG-IFN alfa-2b. Three serious adverse events, including one suicide, might have been related to the study drug [15].

Immediate treatment of patients after diagnosis may mean some patients who would have cleared the infection spontaneously will be exposed to antiviral therapy unnecessarily and may experience treatment-related adverse events. Therefore, treatment strategies involving delayed therapy have also been investigated. In an early pilot study [49], treatment was delayed for 12 weeks after clinical presentation of the disease; patients with detectable HCV RNA then received PEG-IFN alfa-2b (1.5 µg/kg/wk) for 24 weeks [15]. Fifteen of 16 treated patients (94%) attained SVR. Moreover, HCV RNA remained undetectable up to 12 months after therapy discontinuation [49]. Similar results were also reported in a randomized controlled trial in which 129 patients received 12-weeks' treatment with PEG-IFN alfa-2b (1.5 µg/kg/wk) after a clinical observation period of 8, 12, or 20 weeks [16]. The SVR was equivalent in patients treated after a delay of 8 or 12 weeks (95% versus 93%) but was significantly lower in patients treated after a 20-week delay (76%;  $P \leq 0.03$  for both comparisons).

When results were evaluated according to HCV genotype, genotype 1 patients appeared to obtain greater benefit from earlier treatment initiation [16].

Regarding treatment duration, several recent trials have evaluated the efficacy of a short, 12-week course of PEG-IFN therapy [50–52]. In these studies, most patients were asymptomatic and many were intravenous drug users. Patients were treated with PEG-IFN alfa-2b (1.0–1.5 µg/kg/wk) within a median time of 13.5–31 days after peak ALT levels. SVR was attained in 72–74% of patients, and higher rates of SVR (83–92%) were attained by patients receiving higher PEG-IFN alfa-2b dosages (>1.33 and >1.2 µg/kg/wk). This short course of therapy might be particularly useful in difficult-to-treat patients, such as intravenous drug users who typically have more frequent side effects that lead to treatment discontinuation. In the only randomized trial conducted to date, 102 patients with acute hepatitis C who still had detectable HCV RNA after 8–12 weeks of observation were randomly assigned to receive PEG-IFN alfa-2b (1.5 µg/kg/wk) for 8, 12 or 24 weeks. Overall SVR rates were 62%, 82% and 91%, respectively. When analyzing the results according to genotype, patients infected with genotype 1 required a longer period of therapy (24 weeks) to maximize their likelihood of attaining SVR [17]. Finally, on the basis of the limited data in the literature, combination therapy with ribavirin does not result in improved treatment outcomes [30].

In most studies performed to date, response rates appear to be independent of HCV genotype, and patients with genotype 1 have demonstrated results similar to those of patients with genotype 2 or 3 [46,49]. Kamal et al. [16,17] reported a possible lower response rate in genotype 1 patients, but this observation requires confirmation. In the German Acute HCV II trial, baseline HCV RNA was not associated with treatment outcome, but multivariate regression analysis indicated that SVR was correlated with pretreatment ALT levels ( $P = 0.039$ ) [15]. In contrast, in the trial by Calleri et al. [52], the peak viral load before treatment was predictive of SVR in univariate analysis ( $P = 0.0005$ ); they also found that undetectable HCV RNA at weeks 4 and 12 of treatment was predictive of SVR. These preliminary observations indicate that, as in chronic hepatitis C, viral kinetics may become an important predictor of treatment outcome in acute hepatitis C.

### 5.3. Treatment of acute hepatitis C among HIV-co-infected patients

Co-infection with HIV seriously complicates the management of chronic hepatitis C. Co-infected patients experience an accelerated disease course and reduced SVR rates when compared with mono-infected HCV [53–55]. Evidence also suggests that HIV co-infection can alter the disease course and treatment outcome for

patients in the acute stages of HCV infection, but studies are few and patient numbers are small.

Co-infection with HIV renders spontaneous resolution of HCV infection unlikely. In one study of 25 patients with acute hepatitis C and HIV, only one (4%) attained spontaneous resolution. Most of these patients were receiving highly active antiretroviral therapy, and the median CD4<sup>+</sup> T-cell count in this cohort was 345 cells/ $\mu$ l [56]. HIV co-infection may also exert an unfavorable impact on treatment outcome; however, this remains controversial, and data from several small studies report SVR rates ranging from 0% to 71% among co-infected patients receiving PEG-IFN alfa alone or PEG-IFN alfa plus ribavirin for 24 weeks. These studies indicate that no clear clinical benefit is derived by the addition of ribavirin to PEG-IFN alfa-2b monotherapy [56–59]. These SVR rates are generally lower than those observed in patients with acute HCV mono-infection but are higher than those in HIV patients with chronic HCV infection (27–40% [53–55]). Taken together, early antiviral therapy seems to be appropriate in co-infected patients in the absence of contraindications to treatment.

#### 5.4. Treatment of acute hepatitis C among hemodialysis patients

HCV infection is common in patients with end-stage renal disease; estimates suggest that 3–22% of patients undergoing maintenance dialysis may have HCV infection [60]. Little is known regarding the treatment of acute hepatitis C in this population, and only a small number of observational studies have been published [61–63]. In general, these studies demonstrated that IFN alfa or PEG-IFN alfa therapy is effective; each produced SVR rates of 57–86% and was well tolerated [61,62,64,65], but further studies are required.

## 6. Remaining questions and future directions

Recent studies have begun to address several important questions with regard to best treatment practices for patients with acute hepatitis C. Unfortunately, available data lack the robust quality required to develop standardized treatment recommendations. Nevertheless, an abundance of useful information can be drawn from currently published data. Questions that remain unanswered and the current status of ongoing studies are as follows:

1. *When should therapy be initiated?* Data from trials using immediate or delayed treatment strategies (8–12 weeks) have demonstrated high SVR rates ranging from 71% to 94% (Fig. 2). Delaying treatment for 2–3 months after disease onset permits the identification

of patients whose infections spontaneously resolve. Whether an immediate treatment approach is more appropriate in patients with asymptomatic disease or in those infected with genotype 1b still requires confirmation. The German Competence Network for Viral Hepatitis (HEP-NET) [66] is conducting a randomised, controlled trial comparing immediate treatment (PEG-IFN alfa-2b 1.5  $\mu$ g/kg/wk for 24 weeks) at the onset of symptoms with a delayed treatment strategy in which patients undergo a 12-week observation period, after which only those patients who have detectable HCV RNA receive therapy. Asymptomatic patients are entered into an immediate treatment strategy. It is anticipated that the results from this study will help define the most appropriate time to initiate treatment of acute hepatitis C within various subpopulations.

2. *What type of IFN should be administered?* Monotherapy studies with PEG-IFN alfa-2b have yielded SVR rates similar to those reported with conventional IFN alfa. With its once-weekly administration schedule, PEG-IFN alfa-2b or alfa-2a may ultimately become the standard of care in acute hepatitis C treatment, though a head-to-head comparison with conventional IFN would be required to confirm equivalence.
3. *What is the optimal dosage of PEG-IFN alfa-2b?* In the studies of Calleri [52] and De Rosa [51], patients received PEG-IFN alfa-2b doses ranging from 1.06 to 1.66  $\mu$ g/kg/wk. Improved SVR rates were associated with PEG-IFN alfa-2b doses >1.2  $\mu$ g/kg/wk [52] or >1.33  $\mu$ g/kg/wk [51]. These data suggest that the recommended 1.5  $\mu$ g/kg/wk dose of PEG-IFN alfa-2b should be used when treating patients with acute disease.
4. *What is the optimal treatment duration?* At present, the optimal duration of PEG-IFN monotherapy seems to be 24 weeks; however, a 12-week course is also effective in patients treated with a full dosage of PEG-IFN who attain undetectable HCV RNA at week 4. A large, ongoing, randomised, multicentre trial in Italy is investigating the efficacy of shortened treatment duration (12 versus 24 weeks). In this study, all patients with diagnoses of acute hepatitis C undergo a 12-week observation period followed by repeat testing of HCV RNA levels; those with detectable HCV RNA are then randomized to receive PEG-IFN alfa-2b (1.5  $\mu$ g/kg/wk) for 12 or 24 weeks. This study also includes a third treatment arm consisting of combination therapy with PEG-IFN alfa plus ribavirin (>10.6 mg/kg/day) administered over a 12-week period.
5. *Which parameters can be used to predict treatment outcome?* Different baseline parameters, such as gender, age, mode of infection, baseline viral load and HCV genotype, have been analysed by several investigators

and do not appear to correlate with therapeutic outcome [15,49,50,52]. Two studies, however, show poorer virological response in genotype 1 patients than in non-genotype 1 patients, suggesting that genotype may predict treatment outcome [16,17]. These observations warrant further investigation; data from ongoing German HEP-NET and Italian clinical trials should provide more insight into this topic.

6. *How can difficult-to-treat patients be identified and serious side effects be avoided?* A crucial issue for the success of treatment is patient adherence to therapy. In difficult-to-treat patients such as intravenous drug abusers and patients with psychological disorders who are at high risk for early treatment discontinuation [67], indications for treatment must be discussed on an individual patient level. A multidisciplinary approach with effective counseling can be used to inform and motivate patients, thus increasing adherence and averting serious side effects.
7. *Is PEG-IFN plus ribavirin combination therapy more effective than monotherapy?* At present, there is no evidence that the addition of ribavirin improves response rates in patients with acute hepatitis C. It remains to be established whether combination therapy would permit a shortened treatment duration and whether it can provide better results in immunocompromised patients, such as those coinfecting with HIV.

## 7. Conclusions

In conclusion, treatment of acute hepatitis C with IFN alfa offers the opportunity to maximise the rates of viral eradication with SVR in excess of 90%. However, the identification of ideal candidates for treatment, the optimal time for initiating therapy and the optimal dose and duration of therapy require further investigation. Results of ongoing randomised trials will contribute to answering these questions. Surveillance programs designed to monitor populations at high risk represent the best approach for identifying patients with acute hepatitis C. Such programs, together with a standardized approach to treatment, should increase the recognition of acute hepatitis C and the benefits associated with its effective treatment.

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