

REVIEW ARTICLE

Treatment of Acute Hepatitis C

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ABSTRACT

An acute hepatitis C virus (HCV) infection is an uncommonly encountered illness. Patients infected with the HCV commonly tend to be asymptomatic because of spontaneous viral clearance or chronic infection. Early antiviral treatment may be beneficial especially in symptomatic cases. Antiviral therapy with an (IFN)-based regimen is standard except in the instance of a human immunodeficiency virus (HIV) coinfection. The efficacy of HCV therapy has been restricted by the side effects of treatment. Advances in the treatment options of chronic HCV infection have resulted in the development of many new antiviral drugs that may allow for simplified and shortened treatments with increased tolerability and efficacy in patients with acute HCV infection. *J Microbiol Infect Dis 2016;6(1): 40-44*

Key words: Acute hepatitis C, treatment, genotype, interferon, ribavirin

Akut Hepatit C Tedavisi

ÖZET

Akut Hepatit C virus (HCV) enfeksiyonu nadir görülen bir hastalıktır. Hastaların büyük bir kısmı asemptomatik seyretmektedir. HCV ile enfekte olan hastalar virüsü ya spontan olarak temizler veya kronik bir enfeksiyona ilerleyiş söz konusudur. Semptomatik olan hastalarda büyük oranda spontan viral klirens gelişir. Buna karşın asemptomatik hastalarda spontan klirens ihtimali daha düşüktür ve erken antiviral tedaviden fayda görürler. HIV koinfeksiyonu gibi durumlar dışında interferon bazlı rejimler standart antiviral tedavinin temelini oluştururlar. Tedaviden kaynaklanan ciddi yan etkiler HCV tedavisinin etkinliğini büyük ölçüde sınırlamıştır. Kronik HCV enfeksiyon tedavisi alanındaki yoğun çalışmalar sonucunda yeni birçok antiviral ajan geliştirilmiştir. Bu yeni ilaçlar çok daha etkili ve daha iyi tolere edilebildiğinden kronik HCV tedavisi eskiye oranla daha basit ve daha kısa süreli hale gelmiştir.

Anahtar kelimeler: Acut hepatit C, tedavi, genotip, interferon, ribavirin

INTRODUCTION

The annual incidence of the acute hepatitis C virus (HCV) has decreased in recent years, due to effective and comprehensive blood screening practices and increased education programs of high risk groups [1]. An acute HCV infection may be occurred via exposure to the virus through different sources, such as a blood transfusion, injection drug use, sexual transmission, nosocomial transmission, occupational exposures, and inter familial exposure [1]. The greatest risk is related to repeated parenteral exposures in intravenous drug users. HCV transmission risk is lower via needle stick injuries in which health care workers are exposed to the blood or bloody fluids of patients infected with HCV. Despite the transmission rate is low in heterosexual couples, exposure risk is much higher among HIV infected men who have sex with men [2]. The route

of transmission may be related to economic conditions, particularly in developing countries in which HCV infection is primarily associated with health-care-related procedures [1].

For the diagnosis of an acute HCV infection, the presence of both negative HCV antibody and positive HCV ribonucleic acid (RNA) test are required. Besides this positive HCV antibody test after a prior negative HCV antibody test results indicate acute HCV. [3] Monitoring HCV RNA (every 4 to 8 weeks) for 6 months is recommended to determine spontaneous clearance of the HCV infection versus the persistence of infection [4]. Symptomatic identification of patients with an acute HCV infection is uncommon due to its asymptomatic nature [5]. Patients infected with HCV may spontaneously clear the virus or proceed to develop a chronic infection [6]. Several factors influence the treatment efficacy,

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including the regimen, HCV genotype, duration and the initiation of therapy.

NATURAL PROGRESSION OF THE DISEASE

Nearly two thirds of individuals with an HCV infection develop a chronic infection, approximately 20% of patients with chronic infection can develop cirrhosis, and 4% will develop hepatocellular carcinoma [7]. In patients with recently acquired HCV infection may present either asymptotically with mild constitutional symptoms or with an elevated liver function tests. Only 10%–15% of patients are presented with jaundice [5,7]. HCV RNA could be detected within the first two weeks of exposure. 2-6 months or later seroconversion can be detected particularly in high risk populations. During the acute phase of the infection spontaneous clearance is possible [6]. The diagnosis of an acute HCV infection in the presence of an HIV coinfection is often obscured, because the acute HCV infection is more often asymptomatic when compared with HIV-negative patients. Therefore mild elevations in ALT levels should be observed particularly in high risk groups [8].

TIMING OF TREATMENT

Determination of the appropriate timing of therapy in patients with acute hepatitis is difficult, because the exact onset of the disease often cannot be determined accurately except in cases, such as needle stick injuries or unprotected sexual contact, in which the exact time of exposure is known. According to some authors, the presence of ALT elevation with or without clinical manifestations, may be the

ideal time for initiating appropriate treatment [9,10]. Hofer et al proposed that patients should be monitored for HCV RNA with four times over a 12-week period, and patients who remain HCV positive at 12 weeks should receive antiviral treatment [11]. Delaying treatment for 12 weeks helps to avoid unnecessary treatment in patients. In a meta-analysis of 22 studies with 1,075 patients, patients treated within 12 weeks of diagnosis had higher sustained virologic response (SVR) rates than those who initiated treatment between 12 and 24 weeks, or after 24 weeks (83% versus 67% and 63%, respectively) [12]. Initiating therapy earlier than 12 weeks does not appear to be efficacious. Licata et al. demonstrated that delaying the initiation of therapy by 8 to 12 weeks did not decrease the SVR rates [13]. In a study regarding acute HCV treatment, 129 patients were assigned to treatment with pegylated (Peg)-IFN starting at week 8, 12, or 20, and an SVR was achieved by 95%, 93%, and 77% of patients, respectively. No benefit was determined for initiating treatment at 8 weeks compared with 12 weeks for patients with genotypes 2, 3, or 4, although a higher SVR rate was observed in patients with genotype 1 who began treatment at week 8 compared with week 12 [14]. In a randomized, open-label trial including 132 patients with an acute HCV infection, Deterding et al. found the potential benefit of therapy on viral clearance initiated after 12 weeks [15]. Initiation of treatment after 12 weeks may not be inferior to immediate therapy. Treatment approach of patients with acute hepatitis C is demonstrated in Figure 1.

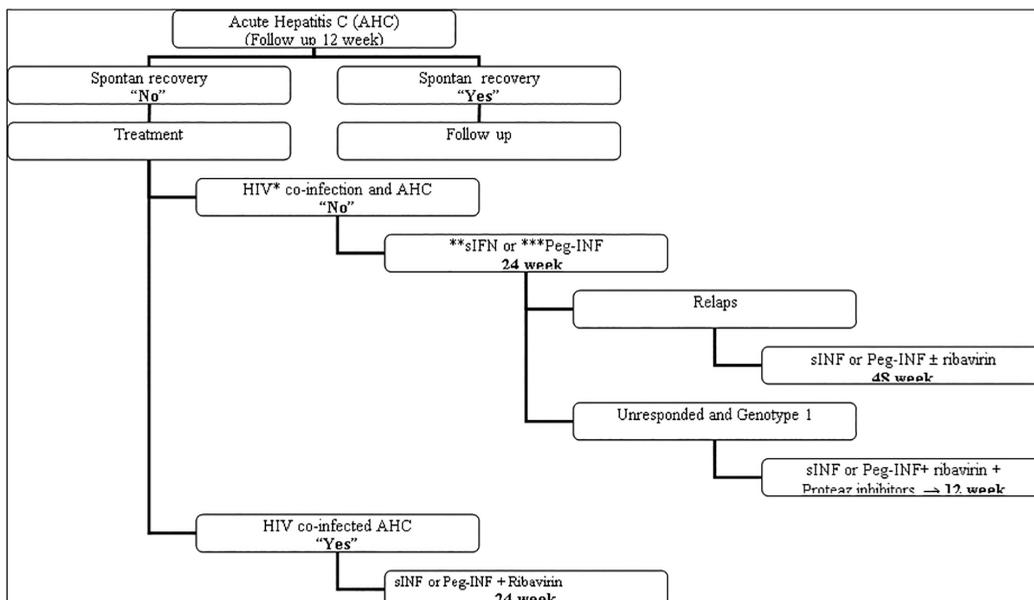


Figure 1. Algorithm for the management of patients with acute hepatitis C

*HIV: Human immunodeficiency virus **sIFN: Standart interferon, ***Peg-IFN: Pegylated interferon

INDIVIDUALIZATION OF THERAPY

Patients must be keen on following the therapeutic regimen, because nonadherence is associated with significant decreases in SVR rates [15,16]. If the patient has certain comorbid conditions, such as a severe depressive illness that is contraindicated in IFN-based therapy, he or she may not be an appropriate candidate. Additionally, intravenous drug users are difficult to treat because of weak adherence to therapy [17].

To improve sustained response rates to IFN-based therapy, drug dose and treatment duration should be modified according to the needs of the patient. Kamal et al. demonstrated that patients with an acute HCV infection who do not have genotype 1 had higher rates of SVR [14]. Virologic response was occurred respectively in 60% and 88% of genotype 1 patients, and in 93% and 100% of genotype 4 patients, after 12 or 24 weeks of therapy. SVR rates could be predicted according to the rapid virologic response rates [18].

Different factors influence treatment outcomes, such as baseline clinical condition, patients ethnicity, adherence to treatment, genotype, and intravenous drug usage history. Therefore, well designed, comprehensive prospective research is needed to clarify the impact of pretreatment and on-treatment viral kinetics of acute HCV infection and to determine the onset, drug choice, and duration of the appropriate drug regimen [1].

TREATMENT OPTIONS

Acute HCV infection should be managed properly because it appears to represent a chance to prevent progression to chronic hepatitis C disease [18]. Early diagnosis and also treatment of an acute HCV infection is likely to decrease the burden of chronic hepatitis, particularly infection with genotype 1 [19]. Additionally, the efficacy of the treatment of acute HCV infection was superior to the treatment of chronic infection [20].

High response rates (>90%) were reported with Peg-IFN- α monotherapy, especially in symptomatic patients, irrespective of the HCV genotypes. In these cases Peg-IFN- α and ribavirin combination does not increase the SVR rate. However this therapy option may be beneficial in patients existing other negative predictors [15,21]. Wiegand et al. reported that treatment duration and SVR rates were independent of HCV genotypes [17].

In the literature, the efficacy of treatment for acute HCV ranged from 22% to 98% with standard IFN given daily or every three days [10,22,23]. A meta-analysis involving 141 patients with acute transfusion-acquired HCV infection treated with standard IFN monotherapy had a greater virologic response when compared with patients who were treated with a placebo or without treatment (42% versus 4%) and a sustained virologic response (32% versus 4%) [24]. A higher SVR rate (98%) with an IFN regimen was demonstrated in the study of Jaeckel et al. Peg-IFN may be preferable, because it is easier to administer and may be better tolerated [22]. Patients who are coinfecting with HIV are the only group that may benefit from the addition of ribavirin therapy. In this patient group, SVR rates are too low with monotherapy [25]. Therefore, adding ribavirin to the regimen may increase SVR rates among patients with HIV infection, but it does not appear to improve outcomes in patients who are infected with HIV. The response rates with Peg-IFN given weekly vary from 57% to 95% [14,16,26]. Although the data that support combining IFN or Peg-IFN with ribavirin are limited in the therapy of acute HCV, a significant advantage over monotherapy with Peg-IFN or standard IFN has not been demonstrated [27,28]. In a multicentered, randomized trial including 148 patients with acute HCV who remained viremic for 12 weeks following the onset of infection, administration of Peg-IFN for 24 weeks, Peg-IFN for 12 weeks, and Peg-IFN plus ribavirin for 12 weeks all resulted in similar SVR rates [28]. However, most studies suggest addition of ribavirin due to increased SVR rates in co-infected patients [8,29].

Direct-acting antiviral agents have not been routinely recommended for the treatment of acute infection, because high SVR rates with IFN monotherapy and disadvantages of side effects with additional agents were observed. Fierer et al. examined combination therapy with telaprevir, Peg-IFN, and ribavirin compared with a standard dual regimen in HIV infected patients with an acute HCV infection and demonstrated higher SVR rates (84% versus 63%) [30].

Guidelines for treatment of acute HCV infections were proposed by the European Association for the Study of the Liver (EASL) that recommend Peg-IFN- α monotherapy (Peg-IFN- α 2a 180 μ g/week or Peg-IFN- α 2b 1.5 μ g/kg/week, for 24 weeks) for patients with acute HCV infection regardless of HIV status. Additionally, patients who fail treatment with the standard treatment options may be retreated with or without ribavirin for 48 weeks. Protease

inhibitor-based triple therapy, including telaprevir and boceprevir should be considered particularly for patients with genotype 1 who failed with standard antiviral therapy [4]. The duration of treatment regimen and response rate of patients with genotype 1 was shown in Table 1.

Table 1. Treatment regimen and response rate of patients with genotype 1

Number of patients	Spontaneous recovery (No/%)	HCV Genotype	Treatment regimen	Duration of therapy (weeks)	SVR Rate (%)	Reference
17	0 (0)	G1 (8/17)	Peg-IFN+ ribavirin	24	100	36
30	9 (30)	G1 (13/26)	Peg –IFN± ribavirin	22±5.7	84.6	18
25	5 (20)	G1 (18/25)	Peg –IFN± ribavirin	24	86.6	37
117	51 (44)	G1 (11/17)	Peg –IFN	12	88.2	38
19		G1 (11/19)	Peg –IFN	12	73.6	19
35	4 (11)	G1 (20/32)	Peg –IFN+ ribavirin	43 (11-72)	75	39
175	27 (15)	G4 (71/156)	Peg –IFN	12	88.3	14
24 (28 episodes)	7 (29)	G1 (23/28)	Peg –IFN± ribavirin	30.7±12	93.7	26
42	7 (17)	G1 (28/42)	Peg –IFN	24	88.5	40

Recently, Pawlotsky suggested that drug regimens such as sofosbuvir with ledipasvir/simeprevir/daclatasvir/ribavirin (\pm Peg-IFN), ritonavir-boosted with paritaprevir, and ombitasvir±dasabuvir, which have demonstrated superiority over conventional therapy for treating chronic hepatitis C, could be alternatives for treating acute HCV infection [31]. Recent treatment options for chronic hepatitis C may present new alternatives that can be used as oral regimens with fewer side effects and increased tolerability and efficacy than IFN and ribavirin [32].

VIRAL CLEARANCE

An HCV infection is self-limiting disease and can spontaneously resolve during the acute period of the infection, or may result in chronic disease. Spontaneous clearance following acute HCV infection is 0-86% within the first 6 months following the infection; therefore, the acute phase of an HCV infection is defined as 6 months following the acquisition of an HCV infection [1,5,9,34]. Patients (%11) who is still viremic at 6 months most probably will clear the virus in the next days [34].

Several factors are predictors of spontaneous viral clearance in the acute stage of the disease female gender, younger age especially children, elevated ALT levels, and acute clinical hepatitis C infection symptoms, particularly jaundice. Symptomatic patients presumably reflect a more effective host immune response which helps to eradicate virus by killing hepatocytes, is responsible for the clinical spectrum of the patients [6,9]. Low

baseline viral load, rapid virologic response rates, being infected with non genotype-1 serotype could be associated with proper treatment outcomes [14]. Other predictors of spontaneous clearance include the presence of hepatitis B virus surface antigen (HBsAg) positivity and host genetic polymorphisms [1,35]. Host factors especially polymorphism of the IL28B gene can be related with spontaneous clearance [18,19]. However, none of these parameters certainly predicts the spontaneous resolution rate of the patients.

IFN based therapy is associated with various side effects, including hematologic, gastrointestinal, dermatological and psychiatric effects including suicide attempts and flu-like symptoms. The side effects of IFN-based regimens are the most encountered difficulties during therapy [35,36].

CONCLUSIONS

An acute HCV infection is rarely encountered clinical condition because of asymptomatic nature of the disease and different rates of spontaneous resolution. Although new treatment options promise dramatic response rates in patients with chronic HCV infection, Peg-IFN-based regimen is still only recommended therapy approach in acute HCV infection.

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