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Acute hepatitis C treatment

Paulo Roberto Lerias de Almeida*

* Secretaria Estadual de Saúde do Rio Grande do Sul, Brazil; Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil.

ABSTRACT

There are no well established treatment guidelines about acute hepatitis C (AHC), leaving physicians to make several challenging decisions, such whether to treat, when to treat and what treatment regimens to use. This article examines the diagnosis of acute infection and critically appraises the various treatment regimens.

Key words. Acute hepatitis C. Hepatitis C virus. Antiviral therapy. Interferon alfa. Pegylated interferon alfa.

INTRODUCTION

Since the 1990s there has been a decline in the incidence of AHC infection in the USA and Europe and this falling incidence is attributed to improved blood donor screening, needle exchange programs and education among injection drug users. Nevertheless, others modes of transmission, including needle-stick injuries among health-care workers, sexual and perinatal transmission have gained importance. Also, unsafe medical practices and contaminated equipments have been identified as major risk factors in areas of high prevalence in developing world.[1]

Recent surveillances for acute viral hepatitis was reported by United States Centers for Disease Control and Prevention (CDC), comparing cases in 2006/2007 with those from previous years.[2,3] AHC declined from 2.5 to 0.3 cases/100.000 population (88%) since the ninety's; however, since 2003 rates have plateaued and injection-drug use was the most common risk factor.

CLINICAL FEATURES

AHC infection is asymptomatic in most patients and only 10-20% of patients were believed to develop jaundice.[4] In patients in whom symptoms are developing, the incubation period between exposure and appearance of symptoms can range from 2 to 12 weeks.[5] Since AHC is encountered infrequently, there are only limited data on the incidence of these symptoms.[1] European studies[6,7] of AHC at tertiary referral centers report high frequencies of symptoms including jaundice(71%), influenza-like illness(64%), dark urine and clay colored stools(36%), nausea or vomiting(35%), and pain in the right upper quadrant of the abdomen(26%). However, these studies could be affected by referral bias, since they were designed to identify HCV infection from a cohort of symptomatic patients.[1] Nevertheless, recent papers from France[8] and Bulgaria[9] revealed the presence of jaundice in 40% and 70% of large series of 126 and 178 AHC infections, respectively. Other series from Japan,[10] Egypt[11] and the USA[12] that have prospectively followed injection drug users or people with needle-stick injury have reported a lower incidence of symptoms, including jaundice (0-10%), and could be more indicative of the overall scenario.

DIAGNOSIS

There is no definitive test to diagnose AHC. An identifiable exposure to HCV, recent seroconversion, marked increases in aminotransferases and exclusion of other causes of acute liver diseases are usually used as circumstantial evidence of AHC. The only method to conclusively diagnose AHC infection is to document seroconversion in a previously seronegative individual. This is most frequently documented in the setting of needle-stick exposure, when the exposed individual is followed prospectively, or during surveillance of high-risk individuals.[1]

After exposure, there is a window of 1-3 weeks before serum HCV-RNA can be detected in serum and

Correspondence and reprint request: Dr. Paulo Roberto Lerias de Almeida
Rua Cel. Aurelio Bitencourt 115 apto 201
Porto Alegre - RS - Brazil - CEP 90430-080
Ph and Fax: 55-51-33325706
E-mail: paulorlalmeida@terra.com.br

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it is the first evidence of HCV infection.[13,14] In older series,[15,16] this window could be up to eight weeks, probably related to less sensitive methods for detection of HCV RNA.

Serum aminotransferases become elevated approximately 4-12 weeks after exposure (range 1 to 26), with variable levels that can include significantly elevated ALT levels (> 10-20 x ULN).[13,14]

Anti-HCV ELISA tests become positive 4-10 weeks after exposure to HCV.[14] Detection of anti-HCV is an unreliable way to identify AHC infection, since the absence of antibodies does not preclude infection in the acute setting: the appearance of antibodies against HCV could be delayed in as many as 30-50% of patients at the onset of symptoms, particularly in immunocompromised hosts.[1,13]

SPONTANEOUS RESOLUTION X DEVELOPMENT OF CHRONICITY

Early studies found that spontaneous virological clearance occurred in about 15-25% of persons who developed transfusion associated AHC and that HCV infection persisted in 75-85%; later, a far higher rate of spontaneous resolution was noted among infected children, young women and even some persons with community-acquired hepatitis C, the figures ranging between 42 and 45%.[17] Even higher rates of spontaneous HCV RNA clearance have been described, as observed on studies of Hofer et al (67%)[18] and Gerlach, *et al.* (52%).[6]

As a general rule, most patients with AHC who are destined to spontaneously clear HCV viremia do so within 12 weeks and usually no later than 20 weeks after the onset of symptoms.[13,14] If viremia persists for more than 6 months, chronic disease should be considered. The possible outcomes of AHC infection are shown in figure 1 and are dependent on many host and viral factors.[1,14] Two German studies suggest that patients who develop symptomatic disease tend to have a higher spontaneous resolution, 52%[6] and 67%.[18] The presence of jaundice might be an indicator of an effective host immune response that leads to spontaneous viral clearance, although this association is not uniform. Others factors that might contribute to spontaneous clearance include genotype 3, female gender, low viral load, white ethnic origin and rapid decline in viral load within the first 4 weeks of diagnosis. By contrast, black ethnic origin, co-existent HIV infection and advanced age could lead to viral persistence.[1]

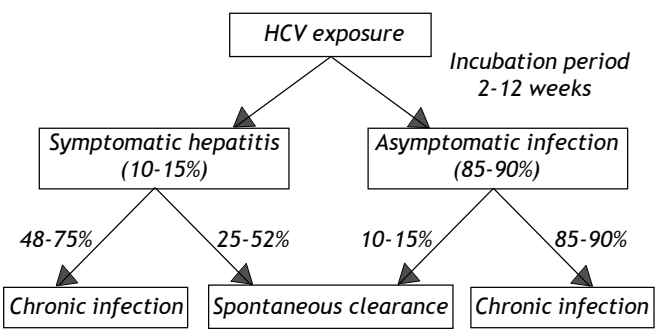


Figure 1. *Outcome of HCV infection.*

TREATMENT

The published studies of AHC show considerable heterogeneity. Most studies are open-label non-comparative investigations with small patient populations that differ widely with respect to design, patient characteristics and treatment regimens; therefore, discerning the most effective intervention remains difficult.[1,5,19] There is a remarkable consistency in the superiority of treatment of AHC in preventing evolution to chronic HCV infection when compared to observation. Two meta-analyses have demonstrated this profit.[20,21] Alberti et al examined the outcome of 369 treated and 201 untreated patients of 17 studies;[20] the pooled data showed a sustained virologic response (SVR) rate of 62% in the treated group x 12% of spontaneous clearance ($p < 0.05$) between untreated individuals. Licata et al.,[21] examined 12 cohort studies reporting data from 162 treated and 81 untreated patients, and found that the likelihood of SVR was 70.5% in the treated compared with 35.3% in the untreated group ($p < 0.05$). Recent published meta-analysis[22] including 1075 patients of 22 studies confirms the evidence: SVR rates for treated patients were 78%, significantly higher than 55.1% of spontaneous clearance rates in the untreated patients (OR=3.08).

Optimal timing of treatment

Early study by Jaeckel, *et al.*,[23] with standard interferon (IFN) recommended immediate therapy for AHC because of excellent treatment responses: SVR 98%; the average time from first signs and symptoms until the start of therapy were 35 days. Waiting some weeks did not reduce the SVR rates as shown by Italian study of Santantonio et al: 28 patients with AHC were followed, 11(39%) had spontaneous clearance and 15 of 16 (98%) patients who

failed to spontaneously clear HCV RNA after12 weeks responded to treatment.[24]

This strategy was also examined in 129 patients[25] with AHC without spontaneously clearance by week 8, by randomized them to begin treatment at week 8, 12 or 20 (43 patients in each group): the SVR was 95%, 93% and 77% when treatment was initiated at week 8, 12 and 20, respectively. Authors suggested that the optimal time to initiate therapy might be week 12, because the response rate dropped off sharply in the group that initiated treatment at week 20. However, in genotype 1 patients the highest SVR was achieved when therapy was started at week 8 (Figure 2); these observation need to be further investigated because all treatments in the current study was administered for 12 weeks.[14,26] Also, Japanese investigators compared the SVR achieved with early initiation of treatment (8 weeks after disease onset) with a delayed treatment strategy (1 year) and demonstrated that the postponed therapy is clearly less effective: 87% and 40% of SVR, respectively.[10]

These studies showed that delaying treatment for 3 months from the time of diagnosis does not have a negative effect on SVR rates, at least in genotypes 2 and 3 patients, and avoids unnecessary treatment for those patients who may undergo spontaneous viral clearance.

There are limited data on the optimal timing for treatment for asymptomatic patients, and it may not be unreasonable to offer immediate treatment to them, because they are less likely to clear the virus spontaneously.

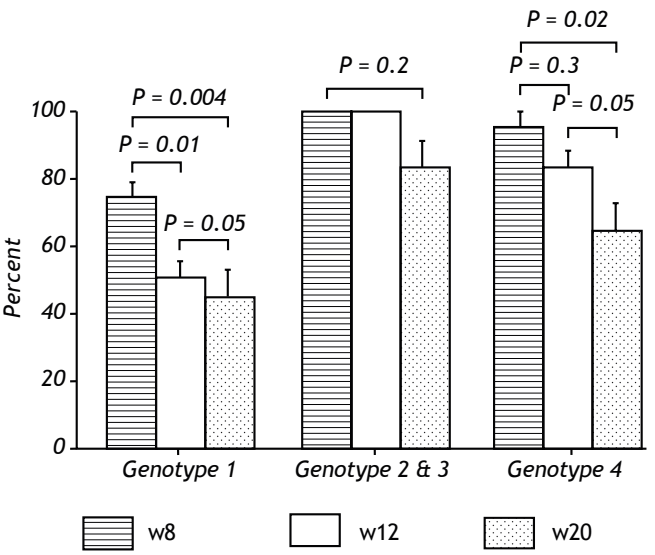
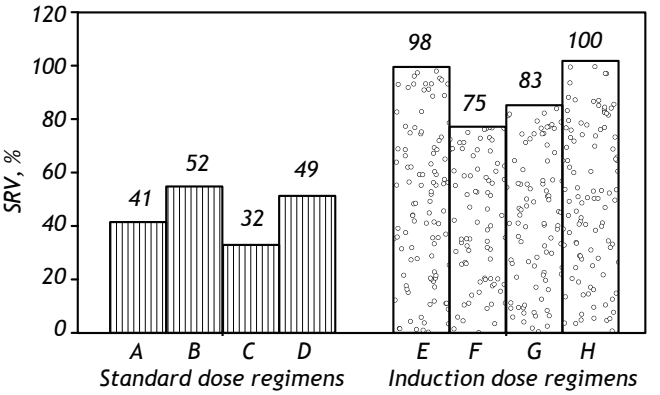


***Figure 2**. Impact of onset of therapy on SVR, according genotypes.*

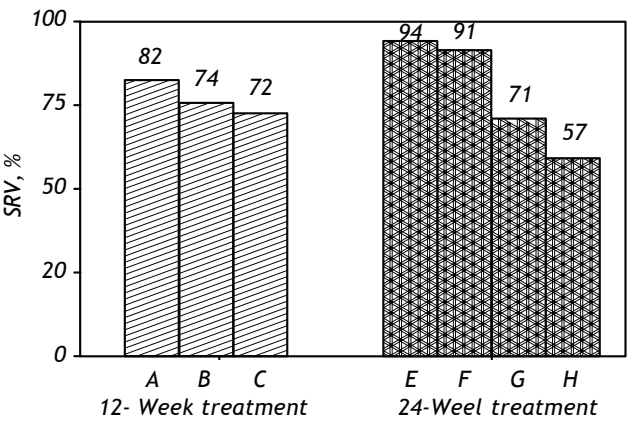
Optimal duration and schedules of treatment (Figures 3 and 4)

Some meta-analyses summarized the results of several small clinical trials of AHC treatment with conventional interferon (IFN), which typically used 3-6 MU administered three times weekly for variable periods of 4-24 weeks. Overall, a modest SVR of 32-52% were obtained [21,26,27,28] (Figure 3).



A Poynard: IFN alfa-2b (3MU TIW) x 3 mo
B Cammà: IFN alfa-2b (3-6 MU TIW) x 4 mo
C Nyers: IFN alfa-2b (3 MU OD or TIW) x 3 mo
D Licata: IFN alfa-2b or 2b (2-6 MU OD or TIW) x 4 wk-6 mo
E Jaeckel: IFN alfa-2b (5 MU/d x 4 wks then 5 MU TIW x 20 wks)
F Delwaide: IFN alfa-2b (5 MU/d x 2 mo)
G Vogel: IFN alfa-2b (10 MU/d until ALT normalization)
H Normura: HLB INF (6 MU/d x 4 wks then TIW x 20 wks)

***Figure 3**. SVR according standard or induction doses regimens of IFN.*



A Kamal: PEG-INF alfa-2b (1.5 µg/kg/wk)
B De Rosa: PEG-IFN alfa-2b (1.0-1.66 µg/kg/wk)
C Calleri: PEG-IFN alfa-2b (1.0-1.5 µg/kg/wk))
E Santantonio: PEG-IFN alfa-2b (1.5 µg/kg/wk)
F Kamal: PEG-IFN alfa-2b (1.5 µg/kg/wk)
G Wiegand: PEG-IFN alfa-2b (1.5 µg/kg/wk)
H Broers: PEG-INF alfa-2b (1.5 µg/kg/wk)

***Figure 4**. SVR with PEG-IFN for 12 or 24 weeks.*

SVR rates increased with higher weekly doses of IFN. The remarkable study of Jaeckel, *et al.*,[23] using an induction regimen of IFN (5 MU/day for 4 weeks, followed by 5 MU three times weekly for another 20 weeks) attained SVR in 43/44 (98%) patients. Shorter treatment durations and high-dose IFN was evaluated by others studies. In two of them, SVR was reported in 21/28(75%) patients receiving 5 MU/day for 8 weeks[29] and in 20/24(83%) patients treated with 10 MU/day until normalization of ALT levels.[30] In a separate study, Nomura et al suggest that a shorter course of daily human lymphoblastoid IFN for 4 weeks could be highly efficacious, with 87% of SVR[10] (Figure 3).

In AHC patients treated with pegylated interferon (PEG-IFN), different strategies have been explored to optimize the SVR (Figure 4). The earlier studies with PEG-IFN also used 24 weeks of treatment: in a large multicenter German study using PEG-IFN alfa-2b conducted by Wiegand et al, 89 patients were treated after a median time from symptoms to therapy of 27 days with the standard dosage of 1.5 g/kg/wk and demonstrated a SVR of 71%;[7] a smaller Swiss study reveal a scarcely SVR of 57% in a group of 14 patients that started treatment between 1 and 50 weeks after the diagnosis.[31] Both studies demonstrated poor adherence with high rates of dropout among intravenous drug users. In contrast, another 24 weeks treatment with PEG-IFN alfa-2b (1.5 g/kg/wk) by Santantonio et al observe a SVR in 15/16(94%) patients that initiate treatment 12 weeks after the diagnosis.[24]

Regarding treatment duration, more recent trials have evaluated the efficacy of a short, 12-week course of PEG-IFN.[32,33,34]Two Italian studies(32,33) use PEG-IFN alfa-2b (1.0-1.6 g/kg/wk) within a median time of 13.5-31 days after diagnosis. SVR was attained in 72-74% of patients, and higher rates of SVR (83-92%) were attained by patients receiving higher dosages (> 1.33 and > 1.2 g/kg/wk).

In the only randomized controlled trial[34] conducted to date, one study compared different durations of therapy in 102 patients with AHC who still had detectable HCV RNA after 8-12 weeks of observation; the patients were randomly assigned to receive PEG-IFN alfa-2b (1.5 g/kg/wk) for 8,12 or 24 weeks. Overall SVR rates were 68%, 82% and 91%, respectively. Treatment for 8 or 12 weeks was effective in genotypes 2, 3, and 4, whereas genotype 1 required 24 weeks of therapy. Multivariate analysis showed that the presence of symptoms, genotype non-1, and rapid virologic response at week 4 were associated with improved viral clearance.

Combination with ribavirin (RBV)

The combination of interferons with RBV has not been tested extensively. The few studies that used RBV associated with IFN[6,35] or PEG-IFN[6,11] found it to be well tolerated, but responses rates were nor significantly higher than with monotherapy.

Treatment of Human Immunodeficiency Virus (HIV) co-infected patients

HIV- infected patients exposed to HCV are less likely to clear the acute infection. Just only 4% and 5% of spontaneous resolution were observed in two more recent series of 25 and 55 co-infected patients.[36,37] There have been few small single center trials of AHC in HIV patients receiving IFN or PEG-IFN, with or without RBV; SVR rates were variable and in general lower than that seen in the HCV mono-infected patients: 0% -71%.[36,38,39,40] A more recent Australian trial with 22 patients treated with PEG-IFN alfa-2a and RBV for 24 weeks showed a SVR of 80%.[41]

CONCLUSIONS

The identification of acute HCV infection represents a unique window of opportunity for achieving high rates of viral clearance. Treatment of AHC with different interferons offers the opportunity of SVR in excess of 90%. A waiting period for observation of 12 weeks is recommended for patients with symptomatic hepatitis to allow for spontaneous viral clearance that can occur at high rates in this subgroup. Asymptomatic and HIV patients may be treated immediately as they are less likely to undergo spontaneous clearance. Treatment durations could vary from 12 to 24 weeks, but recent data on 12 weeks of treatment are encouraging, especially in those who achieve RVR. The role of RBV has yet to be established.

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