

Treatment of Acute Hepatitis C

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Hepatitis C Virus (HCV) infection is a common cause of chronic liver disease but is rarely diagnosed at the stage of acute hepatitis C. HCV becomes chronic in about 85% of individuals and leads to cirrhosis in 5 to 30 percent of cases [1]. The chronic course of acute infection should be avoided to prevent the potential risk of cirrhosis and hepatocellular carcinoma in patients with chronic hepatitis C. Overall, approximately 3% of the world's population is thought to be infected with HCV. In the US, the National Health and Nutrition Examination Study III (NHANES III) showed an anti-HCV prevalence of 1.8% corresponding to 3.9 million anti-HCV-positive patients [2]. In Germany, approximately 350,000 individuals (0.4% of the population) are HCV carriers [3].

EPIDEMIOLOGY OF ACUTE HEPATITIS C

HCV is a blood-borne virus. Until 1990, hepatitis C was the most important post-transfusion hepatitis, but the epidemiology of HCV infection has changed dramatically. Nowadays, most patients with acute HCV infection are intravenous drug users. The risk of acquiring HCV by blood products has been reduced to less than 1/500,000. In Germany all blood products are screened for HCV RNA by PCR and thus, the risk of acquiring HCV through contaminated blood is close to zero.

NATURAL HISTORY

Regarding the acute phase of hepatitis C infection, it is currently estimated that 25-30% of people infected with HCV will clear the virus spontaneously 2-6 months after acquiring infection. Although there is no way of predicting viral clearance on an individual basis, it has been suggested that people with clinical symptoms of acute hepatitis (e.g. jaundice), are more likely to clear the virus [4]. These data support the findings of Gerlach et al. [5], and Nomura et al. [6], showing that symptomatic icteric patients more often clear the virus spontaneously than asymptomatic individuals. In the Nomura trial the incidence of spontaneous HCV clearance during the first two months was rather low (12% of cases), compared to other recent trials. The rate of spontaneous clearance of HCV in acute hepatitis C was also analysed by Hofer et al. [7] in a recent study. 75% (n=12) of patients with acute icteric hepatitis showed clearance of HCV in a repeated testing of HCV viral load. The authors concluded that early HCV viral kinetics are a useful tool for distinguishing between patients who require treatment and those who do not. Moreover, Lehmann et al. [8] suggest that spontaneous clearance of HCV may be higher in patients with HCV genotype 3 than in HCV genotype 1. There are also results suggesting that women, babies and young adults are also more likely to clear the virus than men [9].

DIAGNOSIS OF ACUTE HEPATITIS C

The symptoms of acute hepatitis C are usually mild and variable, and can include malaise, nausea, loss of appetite, weakness, abdominal discomfort, pale stools and dark urine. However, most patients do not have clinical symptoms or jaundice in the phase of acute viral infection and clinical symptoms are not different from other types of hepatitis. The asymptomatic patient is often detected via surveillance, such as following needle-stick exposure to a known carrier. Moreover, there is still no prophylactic vaccine for HCV.

Unfortunately, there is no specific diagnostic test to identify acute HCV infection, to distinguish it from reactivation phases that may occur in chronic infection and to predict spontaneous clearance in patients with acute HCV. Without an accepted serologic definition of acute hepatitis C, and because many individuals do not have a previously documented negative anti-HCV test, the diagnosis of acute

HCV is usually based on surrogate markers (e.g. the existence of a potential infection event, previously normal ALT values, exclusion of other liver diseases etc.). Thus acute hepatitis C has been difficult to study and there is still limited information about its natural history and optimal management strategies.

TREATMENT OF ACUTE HEPATITIS C

Unlike the treatment of chronic hepatitis, controlled trials and practice guidelines for the treatment of acute HCV are lacking. The NIH Consensus Conference stated that treatment of acute hepatitis C “is warranted” [10], and several meta-analyses of published studies have concluded that antiviral therapy during acute HCV infection significantly reduces evolution to chronic hepatitis [11]. This was supported by the 2003 German Hep-Net/DGVS consensus conference, which advises antiviral treatment of acute hepatitis C with interferon for 24 weeks, to prevent chronicity.

Several studies have assessed treatment with interferon in patients with acute hepatitis C, but there are problems with the accurate timely diagnosis of acute HCV and thus the comparison of research results. Different variables of the studies are represented in Figure 1. Furthermore, randomized controlled trials are difficult to perform, because of problems with patient enrolment, such as in patients with intravenous drug addiction, ethical issues, and the small number of people diagnosed with acute HCV.

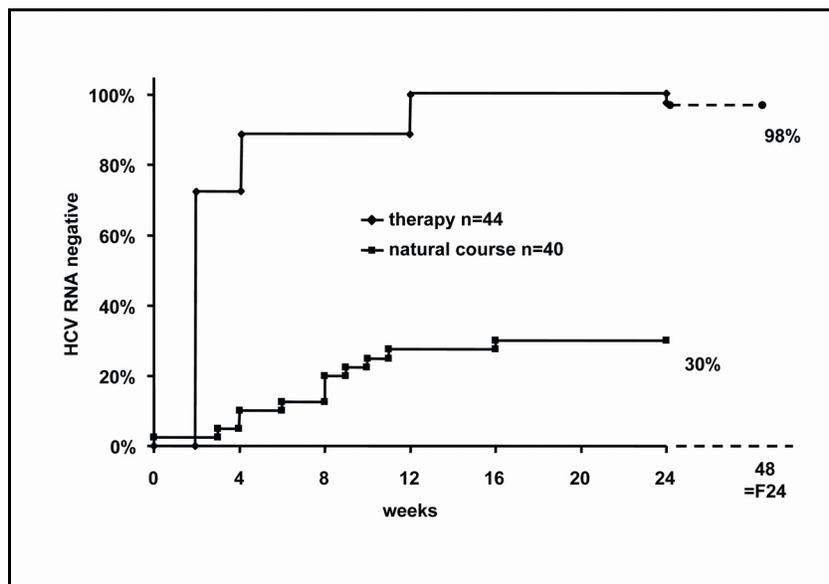


Figure 1: Early treatment of acute HCV-infection. Santantonio et al. (Bari, Italy).

In order to standardize and optimize treatment of acute HCV, we performed a prospective controlled trial in 1998 in Germany [12, 13] and showed that monotherapy with interferon-alpha-2b for 24 weeks prevented chronicity of acute hepatitis C in 98% of cases (n=44 patients).

One issue is when to begin treatment? Should treatment of acute HCV be delayed 2-3 months after diagnosis or started immediately? Starting immediately seems reasonable, before the infection is established. In the Jaeckel study the favorable outcome of patients with acute HCV could be due to the fact that treatment was started a mean 89 days post-infection. In other studies [6, 7], a good starting point for therapy in HCV-infected, HCV RNA-positive patients was between day 70 and 100 after exposure, corresponding to day 20-50 after the onset of symptoms. Nevertheless, in the Jaeckel trial [12] one

third of patients who were treated might have cleared the virus spontaneously before starting treatment.

To study the efficacy of pegylated interferon in acute hepatitis C, a second German trial was started in February 2001 with pegylated interferon-alpha-2b alone for 24 weeks. Results were similar in this study to those in the Jaeckel study with virological response rates of >90% at least in the protocol analysis [14].

Thus far, there are no available data on the efficacy of antiviral therapy for asymptomatic acute hepatitis C. While many uncertainties remain, there are clear guidelines for management after injuries with HCV-contaminated needles [15]. All expert panels agree that there is no rationale for immediate post-HCV-exposure prophylactic treatment as is currently performed after HIV exposure. Monthly monitoring of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and a single measurement of the HCV RNA with PCR after 4-8 weeks are sufficient (Figure 2). Overall, it has been estimated that only 1-3% of needle stick injuries lead to infection.

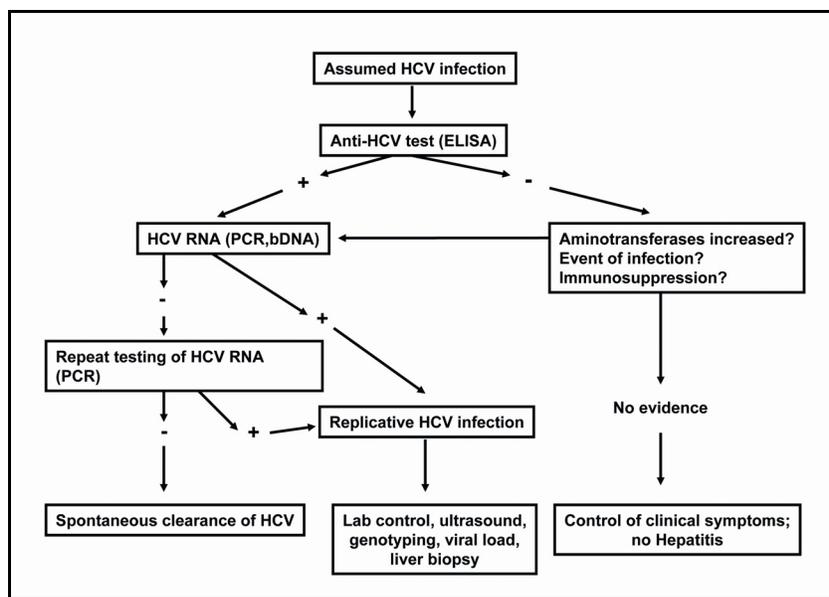


Figure 2: Diagnostic algorithm.

PERSPECTIVES

Numerous uncertainties remain about treatment of acute hepatitis C infection. When is the best time to start therapy; when the patient is first HCV RNA-positive before the onset of symptoms, at the peak of ALT elevation, or when HCV RNA is already declining? Or even later, after waiting for spontaneous HCV clearance, so that only persistently viremic patients undergo treatment? Because the only available data are for symptomatic acute HCV infection, the best treatment regimen for asymptomatic individuals is unknown. Should patients infected with HCV genotype 2 or 3 be treated since chronic HCV with genotype 2 or 3 can be cured in more than 50% of patients? What role should interferon therapy play in intravenous drug abuse patients, methadone substitution programs or concurrent infections with HIV or HBV?

In order to obtain new data about the advantages of the “wait and see” strategy on one hand, and immediate treatment, on the other, a nationwide upcoming randomised trial by the German network of excellence for viral hepatitis (Hep-Net: www.kompetenznetz-hepatitis.de) will compare these two treatment strategies (Figure 3). It is our hope that this Hep-Net acute hepatitis C III trial will provide answers to most of these open questions.

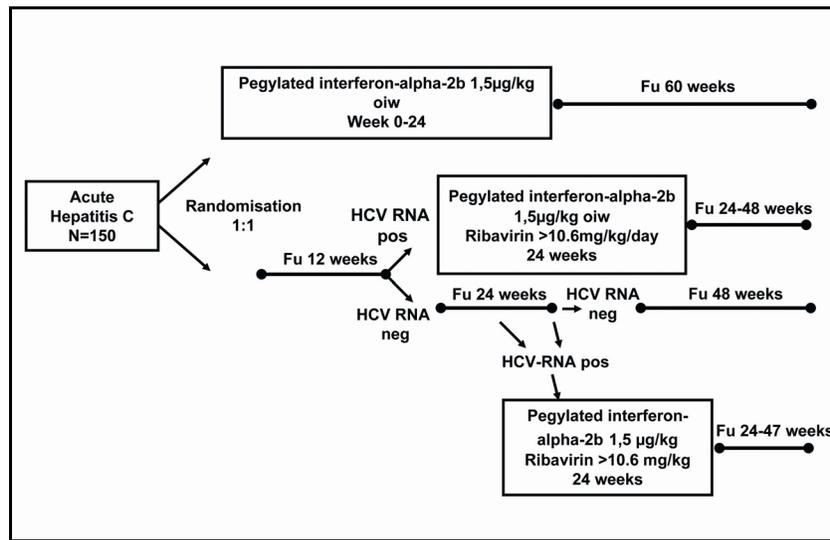


Figure 3: Immediate monotherapy vs. delayed combination therapy. Acute hepatitis C No. 3 Trial by the German Network of Viral Hepatitis “HEP-NET” www.kompetenznetz-hepatitis.de.

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