Journal of Hepatology Update: Hepatitis C

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Natural history of hepatitis C

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Clinical Course

Summary

There has long been evidence that hepatitis C can lead to persistent infection in a high proportion of infected individuals, and can progress to chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC). The transition from acute to chronic hepatitis C is usually sub-clinical. Accurate studies of the time course for clearance of acute hepatitis C are difficult to carry out because of the silent onset of the acute disease. The likelihood of spontaneous HCV resolution is associated with several genetic factors, including *IL28B* inheritance and the DQB1*0301 allele of the major histocompatibility complex class II. Most data suggest that resolution in the acute phase without progression to chronic disease is not accompanied by significant disease, but minor histological lesions have been observed in anti-HCV positive, HCV RNA negative individuals. The risk of reinfection remains a possibility after clearance of acute hepatitis C. High rates of sexually-transmitted infection are being reported in HIV positive men who have sex with men (MSM). Chronic infection with HCV is the leading cause of end-stage liver disease, hepatocellular carcinoma (HCC) and liver related death in the Western world. The natural history of the chronic disease remains incompletely defined. It is generally a slowly progressive disease characterized by persistent hepatic inflammation, leading to the development of cirrhosis in approximately 10–20% of patients over 20–30 years of HCV infection. However, the published data indicate varying progression rates to cirrhosis. Overall, once cirrhosis has developed there is a 1–5% annual risk of HCC and a 3–6% annual risk of hepatic decompensation. Following an episode of decompensation the risk of death in the following year is between 15% and 20%. The high number of chronically infected individuals, the burden of disease, and the absence of a vaccine indicates that treatment will form part of the disease control but the impact, effectiveness and outcomes of treatment in various groups remain uncertain. Several studies and meta-analysis have concluded that eradication of HCV with antiviral therapy reduces the risk of HCC in patients with chronic hepatitis C, independent of fibrosis stage, but the risk is not eliminated.

Introduction

Non-A non-B hepatitis was formerly identified as a putative viral hepatitis occurring after transfusion of blood products or intravenous drug use. There was evidence that non-A non-B hepatitis could lead to persistent infection in a high proportion of infected individuals, and could progress to chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC). HCV was discovered to be the major cause of non-A non-B hepatitis in 1989, and is now known to be a leading cause of chronic liver disease in both industrialised and developing countries. Within Europe the sero-prevalence increases with age with a peak prevalence occurring in 55–64 year old patients; Southern and Eastern Europeans have the highest peak prevalence [1].

The high number of chronically infected individuals, the burden of disease and the absence of a vaccine indicates that treatment will form part of the control of the disease. However the majority of those with persistent infection are unaware of the infection, and screening programs to identify patients will be required to prevent silent progression of the disease [1,2]. The high prevalence and incidence of hepatitis C necessitates that treatment to prevent disease forms part of the perceived strategy to limit control of the disease, but the impact, effectiveness and outcomes of treatment in various groups remains uncertain. The overall impact of treatment for patients with mild or advanced disease may differ, and the effect of widespread treatment on the future burden of disease will need ongoing evaluation, particularly to reduce the prevalence of infection and disease.

Keywords: Chronic hepatitis C; Acute hepatitis C; Natural history of hepatitis C; Antiviral treatment; Liver transplantation; Interferon; Direct acting antivirals; Cirrhosis; Hepatocellular carcinoma.
Received 26 May 2014; accepted 10 July 2014

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Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ALT, alanine aminotransferase; HIV, human immunodeficiency virus; PCR, polymerase chain reaction; INF, interferon; RBV, ribavirin; PEGINF, pegylated interferon; SVR, sustained virological response; PWID, people with injecting drug use; MSM, men who have sex with men; HBV, hepatitis B virus; LT, liver transplantation; CyA, cyclosporin; CNI, calcineurin inhibitor; MELD, model for end stage liver disease.

Key Points

Acute hepatitis C

- Up to 4 million people are newly infected with HCV annually
- The acute illness is clinically mild and is typically unrecognised and undiagnosed
- Between 18-34% of infected individuals spontaneously clear HCV
- Acute resolution of HCV is not associated with any long-term sequelae
- Treatment is indicated in patients who are deemed to develop chronic hepatitis

Chronic hepatitis C

- Is the leading cause of end-stage liver disease, hepatocellular carcinoma and liver related deaths in the Western world
- The effects of chronic hepatitis C extend beyond liver related morbidity and impact on the overall quality of life
- Fibrosis progression rates are extremely variable and are influenced by host, viral and environmental factors
- Achievement of a sustained virologic response (SVR) is associated with a reduction in portal hypertension, hepatic decompensation, hepatocellular carcinoma and liver related mortality
- Following liver transplantation fibrosis rates are accelerated with graft cirrhosis rates of 30% at 5 years

Acute hepatitis C

Populations at risk of acute hepatitis C are patients who received blood transfusions, blood products or anti D immunoglobulin in pregnancy prior to 1990, before routine screening of blood products for HCV, intravenous drug users and intra nasal cocaine users, patients with tattoos or body piercings, heath care workers, dialysis patients, and those partaking in high risk sexual activities. Since the introduction of routine screening of blood products and sterile injection needles the principal cohorts of newly infected patients has changed. The majority of patients presenting as new cases in developed countries now are people who inject drugs and men who have sex with men [3]. Estimates of the annual incidence indicate that three to four million persons are newly infected each year and 350,000 people die annually from HCV related causes [4]. The acute illness is clinically mild and typically unrecognised and thus, it is only infrequently diagnosed, particularly in those who progress to chronic hepatitis. After six months of persistence of HCV RNA within the blood the infection is defined as being chronic. The transition from acute to chronic hepatitis C is usually sub-clinical. The initial features of the acute illness are non-specific flu-like symptoms. They are not diagnostic of HCV in particular, as they are common to many acute viral infections. More specific symptoms of viral hepatitis can be encountered in a minority of individuals: jaundice, dark urine, anorexia, aversion to smoking among smokers and abdominal discomfort may occur. Physical findings are usually minimal, apart from jaundice in a third of patients. Chronic hepatitis is the most common outcome, usually characterized by raised serum aminotransferases and may lead to fibrosis and cirrhosis in the liver. Thus chronicity is the major complication of acute hepatitis C.

Accurate studies of the time course for clearance of acute hepatitis C are difficult to carry out because of the silent onset of the acute disease. Studies to determine the rate of persistence are few and may be biased by the mode of ascertainment. They frequently involve the prospective study of symptomatic individuals, who are more likely to clear the virus [5,6]. Asymptomatic individuals are more difficult to identify for obvious reasons. In the studies that are available, it is frequently stated that 15–40% of individuals resolve their acute disease and do not progress to chronic hepatitis, based largely on retrospective studies of post-transfusion hepatitis. This range points to a degree of uncertainty. Factors such as the immune response, determined by host genetics, gender, mode of acquisition, the severity of the acute illness, presentation with jaundice, a poorly defined weak immune response, immunosuppression with for example corticosteroid treatment, which can affect clearance of HCV, HIV co-infection, are all determinants of the acute response. This means that the time course of clearance is difficult to establish with certainty. The likelihood of spontaneous HCV resolution is associated with several genetic factors, including *IL28b* inheritance and the DQB1*0301 allele of the major histocompatibility complex class II2 [5,7,8].

Grebely *et al.* showed among 632 individuals with acute hepatitis C that spontaneous clearance occurred in 173 of 632, and at 1 year after infection, 25% had cleared HCV [6]. Among those with clearance, the median time to clearance was 16.5 weeks with 34%, 67%, and 83% demonstrating clearance at 3, 6, and 12 months. Female sex was associated with clearance. Although there have been few opportunities for longitudinal studies of acute hepatitis, those which are available show considerable variance: a review of 675 individuals showed that clearance of infection ranged from 0% to 80% with a weighted mean of 26% [9]. Females were more likely to clear than males (40% *vs.* 22%) and patients with identified clinical infection were more likely to clear than those that were identified through serological incidence studies (revealed by seroconversion from negative to positive anti-HCV) (31% *vs.* 18%). Wang *et al.* indicated that 18% of 67 individuals had spontaneously cleared hepatitis C after 6 months of follow up [9]. Yeung *et al.* showed that 28% of 157 children cleared HCV [10]. Importantly Cox *et al.* studied 179 anti-HCV negative injection drug users [11]. After prospective evaluation 62 (34%) had seroconverted to anti-HCV. HCV RNA was measured by Cobas Amplicor test (RT PCR) and by transcription mediated amplification (TMA, Chiron). Detectable RNA typically preceded detection of the antibody by 5–6 weeks and HCV RNA detection typically preceded elevation of ALT [11]. In a subset of the cohort, 20 patients cleared viraemia. Viral recovery was defined as the presence of anti-HCV antibody with HCV RNA undetectable by the COBAS assay obtained during at least 2 consecutive visits more than 300 days after initial detection of viraemia. Their paper illustrates several patterns of viraemia during acute hepatitis C. No