The natural history of hepatitis C virus infection

Mohammed N. Al-Quaiz, *MD, MRCP(UK),* ***Tariq A. Madani****, MD, FRCP(Can),* ***Mohamed A. Karawi,*** *MD.*

ABSTRACT

Chronic hepatitis C virus (HCV) infection is a major health problem worldwide. The natural history of HCV infection is not fully understood. For years, there has been an overestimation of the rate of chronicity in acute HCV. Similar high rates of progression to cirrhosis in chronic HCV were reported. The source of confusion stems from the fact that most acute HCV infections are asymptomatic and never come to medical attention. The consequence of this is that most early studies of natural history reflect the more severe end of the spectrum of the disease. Recent studies reported 43-45% rate of chronicity as opposed to the old rates of 77-85%. Also, the rate of progression to cirrhosis and hepatocellular carcinoma was found to be much lower than previously reported. Multiple factors contribute to the chronicity and progression to cirrhosis, the most important being male gender, age, alcohol intake, and the degree of liver fibrosis on initial biopsy. At least 38% of patients with HCV will manifest symptoms of at least one extrahepatic complication. The most important extrahepatic manifestation is mixed cryoglobulinemia. Other extrahepatic manifestations and their response to antiviral therapy are discussed.

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Hepatitis C virus (HCV) is well recognized as a major health problem, with a prevalence rate of around 3% worldwide. It is the most common cause of liver cirrhosis and hepatocellular carcinoma. The natural history of HCV is however, not fully understood. Multiple factors contribute to this uncertainty, the most important of which, is the fact that most acute HCV infections are asymptomatic.[1] It has become clear that the clinical studies of natural history may have reflected the course of the more severe end of the spectrum of this disease. Early studies of the natural history of HCV came from follow up of cases of non A, non B (NANB) hepatitis.[2] Since the discovery of the HCV virus and the introduction of specific diagnostic tests, it became evident that most of the post-transfusional and sporadic NANB hepatitis are caused by HCV.[3-6] Nonetheless, some post-transfusional and sporadic NANB hepatitis and most of the fulminant NANB hepatitis are negative for HCV antibodies and HCV-ribonucleic acid (RNA).[7,8] Knowledge of the natural history of the HCV is critical in order to decide on the optimum therapeutic options and to provide the patient with the correct information regarding the progression of the disease. For simplicity we will divide the natural history of HCV into 3 categories, acute HCV, chronic HCV, and extrahepatic manifestations.

Acute hepatitis C infection. Patients who sustain acute HCV infections are typically asymptomatic. Only 20% of them become clinically jaundiced. The primary HCV infection is poorly characterized, and most of the clinical picture of acute hepatitis C has mainly come from post transfusion infection. Transition from acute to chronic hepatitis and evolution to cirrhosis almost always occurs in the absence of symptoms.[9] The symptomatic onset of acute HCV infection varies between cases with a range of 3-12 weeks after

From the Department of Medicine (Al-Quaiz), King Faisal Specialist Hospital & Research Centre, Department of Gastroenterology (Karawi), Armed Forces Hospital, Riyadh and the Department of Medicine (Madani), King Abdul-Aziz University, Jeddah, *Kingdom of Saudi Arabia*.

Address correspondence and reprint request to: Dr. Mohammed N. Al-Quaiz, Consultant Hepatologist, King Faisal Specialist Hospital & Research Centre, PO Box 3549 (MBC # 46), Riyadh 11121, *Kingdom of Saudi Arabia*. Tel. +9665 5472638. Fax. +966 (1) 4427499. E-mail: mquaiz@hotmail.com

exposure.[10] In self limited acute hepatitis C, symptoms last for several weeks and subside as alanine transferase (ALT) and HCV-RNA levels fall. Acute hepatitis C can be severe and prolonged but is rarely fulminant.[10] Almost one third of patients have negative anti-HCV antibodies at the onset of symptoms.[11] Nonetheless almost all patients will eventually be positive for HCV antibodies. Some patients have low titer for HCV antibodies and will lose any evidence of all markers of previous HCV infection after recovery.[12,13]

Although patients produce high titers of antibodies to different components of the HCV virus genome, none of these antibodies seem to protect against the virus or to alter the course of the disease. Hepatitis C virus RNA will be detected in the serum within 1-2 weeks after exposure in almost all patients. Hepatitis C virus-RNA serum concentration will rise rapidly in a few weeks and then peak more gradually to 10^5-10^7 IU/ml.[10] During convalescence, the HCV-RNA will be lost in some patients and will continue to be negative thereafter, whereas in others the virus persists leading to chronic HCV infection. As the transitional phase of acute to chronic HCV infection may become intermittently negative for HCV-RNA, more than one negative HCV-RNA test is required to confirm the clearance of the virus.

There had been an overestimation of the rate of chronicity after acute HCV infection. Most studies reported a high rate of progression to chronic disease and fibrosis (77-85%).[9,10,14-17] These figures seem to reflect the progression in individuals at the referral centers rather than the actual natural history of the acute infection. The Irish Hepatology research group found a high frequency of spontaneous resolution (45%) and low prevalence of cirrhosis in an analysis of a cohort over a 17-year follow up period in young females who were infected by anti-D immunoglobulins contamination.[18] Similar results were reported by other groups.[19-21] Furthermore, lower rate of chronicity (43%) had been reported by Larghi et al.[22] The mechanism of chronicity is not known. Several factors were thought to unfavorably influence the outcome of acute HCV infection, the most important of which are male gender, age more than 40 at time of infection, and human immunodeficiency virus (HIV) co-infection. Viral factors including viral dose, genotype, and quasispecies do not seem to alter the outcome of acute HCV.[10]

Chronic hepatitis C infection. Chronic hepatitis C is marked by persistence of HCV-RNA for at least 6 months after the onset of acute infection. During the evolution of acute to chronic HCV infection, HCV-RNA and ALT can fluctuate markedly. As much as 25% of patients who develop chronic HCV infection have periods during which, they have undetectable HCV-RNA and normal ALT.[10] Once chronic infection is established, HCV-RNA tends to stabilize.[1] The mechanism by which HCV virus causes chronic progressive liver damage is not known. Several factors have been associated with more progressive course of the disease towards fibrosis, cirrhosis, and hepatocellular carcinoma.[10,15,23,24] Male gender is significantly associated with progression to fibrosis.[18,19,23] The chronicity rate was 30% in subjects below the age of 20 years and 76% in those older than 20 years.[25] In post transfusion hepatitis, patients over the age of 40 years at the time of onset of infection have poorer prognosis with at least 20% of patients developing cirrhosis in 15-20 years.[26,27] Daily alcohol consumption of more than 50 grams is associated with more progressive disease.[23,28] Immune deficiency and co-infection with HIV are also known to be associated with worse disease and rapid progression to cirrhosis.[29] Patients with higher histological activity index at initial liver biopsy, and persistently elevated ALT (serum ALT level more than 5 times normal) had more advanced fibrosis.[30] African Americans had been shown to have a more benign clinical outcome than Caucasian Americans.[31,32] Virological factors, such as the level of viremia, HCV genotype, and the presence of a high quasispecies heterogeneity have not been associated with the rate of progression.[33]

As many as 20% of patients with chronic HCV infection go on to develop cirrhosis in the first or second decade of HCV infection **(Figure 1)**. Hepatocellular carcinoma may develop in as many as 1-4% per year of patients with established cirrhosis.[9] Estimates of standardized mortality rates show differences between annual mortality rates in cirrhotics (3.9%) and non-cirrhotics (0.9%).[34] In patients with HCV related chronic hepatitis and persistently normal ALT levels, the grade of disease activity does not increase over years and progression to cirrhosis is slow or absent.[35]

Extrahepatic manifestations. Patients with chronic HCV infection may develop various extrahepatic complications. At least 38% of patients with HCV will manifest symptoms of at least one extrahepatic complication.[36] Hepatitis C virus positive patients with high serum gamma-globulin or high total bilirubin are at high risk of multiple extrahepatic complications.[37] The pathogenesis of these extra-hepatic complications is not well understood. The most common extrahepatic manifestation is mixed cryoglobulinemia (IgG, IgM, or both). Approximately 40% of patients with chronic HCV develop detectable serum cryoglobulins or cryoprecipitates and HCV is reported in 30-98% of patients with mixed cryoglobulinemia.[38,39] Although the natural history of HCV-associated cryoglobulinemias is not known, in the absence of therapy it can progress to severe vasculitis and or renal failure.[23] The most common renal disease associated with chronic HCV is membranoproliferative glomerulonephritis with or without cryoglobulinemia. Some patients with long standing cryoglobulinemia seem to be at risk for developing B cell non-Hodgkin lymphoma. **Table 1** lists the most important extrahepatic manifestations associated with chronic HCV infection.[35-41]

In conclusion, despite advances in diagnostic and therapeutic aspects of HCV infection, the natural history of this disease remains to be further elucidated.

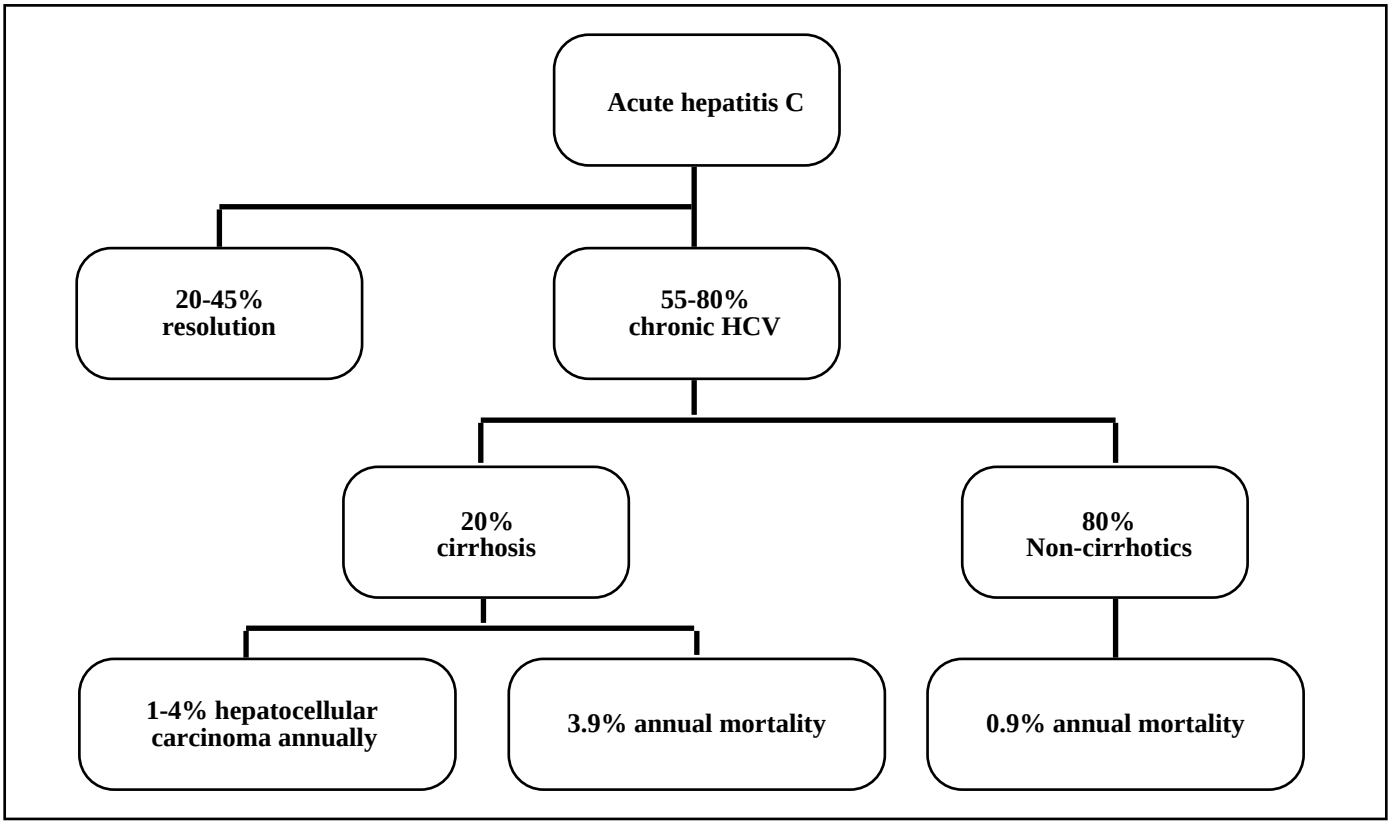

Figure 1 - Natural course of hepatitis C virus (HCV) infection.

Table 1 - Extrahepatic manifestations associated with chronic hepatitis C infection and the effect on interferon therapy.

Manifestation	Effect of interferon therapy
Hematological	
Mixed cryoglobulinemia	Improvement
Thrombocytopenia	Deterioration
Non-Hodgkin lymphoma	Improvement
Aplastic anemia	NA
Endocrine	
Hyperthyroidism, hypothyroidism	Deterioration
Hashimoto's thyroiditis, thyroid antibodies	Deterioration
Diabetes mellitus	NE
Renal	
Glomerulonephritis	Improvement
Dermatological	
Porphyria cutanea tarda	NE
Lichen plannus	Mixed
Leukocytoclastic vasculitis	Improvement
Malacoplakia	NE
Others	
Sjogren's syndrome	NE
Seronegative arthritis	NE
CREST	NE
Pulmonary fibrosis	NE
Moorhen's corneal ulcers	Improvement
Cerebral involvement	Improvement

NA - not applicable, NE - no effect, CREST - Calcinosis, Raynaud's, phenomenon, Esophageal dysfunction, Sclerodactyly, Telangiectasia

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