Natural History of Hepatitis C and Prognostic Factors of Disease Progression

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Infection with the hepatitis C virus (HCV) is one of the main causes of chronic liver disease, cirrhosis and hepatocellular carcinoma worldwide, and is particularly prevalent in Western countries. Acute infection with HCV is often asymptomatic or mild but progresses to chronic infection in more than 50% of the cases. Chronicity rates vary widely and are influenced by many factors, which are mainly related to the host rather than to the virus itself. These include age, immunocompetence and genetic background. There are approximately 170 to 200 million HCV chronic carriers worldwide and most of them are asymptomatic and thus not yet identified. The prevalence of HCV infection in the general population varies greatly in different parts of the world, and is estimated to be between 0.1 and 5%, with a peak prevalence of as high as 20 to 25% in Egypt. According to current estimates, nearly 2 to 4 million individuals in the US and more than 5 million people in Western Europe are chronically infected with HCV. Many have not yet been diagnosed, because of lack of symptoms and major risk factors. Thus, it is expected that many HCV carriers will be diagnosed in the near future and will come to medical attention. This is mainly because of increasing interest in HCV infection from patient advocacy groups, public health advisory boards and institutions that have raised the issue of the "silent epidemic" of HCV and are encouraging individuals at risk to be tested.

The natural history of chronic HCV infection varies greatly and is only partially understood. The rate and speed of progression from initially mild to severe, advanced disease and to end-stage complications vary markedly from individual to individual and are strongly influenced by a number of co-factors. Because of this and because the disease progresses rather slowly and for decades even in the most rapidly evolving cases, it has been difficult to obtain observational data covering the whole course of chronic disease. Thus, the natural history of HCV infection is usually represented as a series of disease stages through a multi-stage model formulation derived from evidence-based transition rates between specific stages [1-5]. This multistage modeling approach predicts that around 20 to 40% of patients with chronic hepatitis C will progress to end-stage liver disease during their lives and that around 10 to 20% will die of liver-related causes. Outcome modeling of the natural cause of hepatitis C is useful for assessing the future burden of the disease in the general population and in specific patient cohorts as well as for economic studies evaluating the cost-effectiveness of different interventional strategies and algorithms. However, to obtain information to assess the prognosis in individual cases in clinical practice, it is more useful to describe the progression rates and outcomes observed in published studies for the main clinical categories of HCV carriers. These include: a) HCV carriers with persistently normal alanine amino-transferase (ALT); b) histologically mild chronic hepatitis C; c) moderate to severe chronic hepatitis C; d) HCV-positive compensated cirrhosis; e) HCV carriers with extrahepatic manifestations.

LIVER DISEASE AND THE OUTCOMES IN ASYMPTOMATIC HCV CARRIERS WITH NORMAL ALT

Recent population-based studies indicate that around 40% of individuals with chronic HCV have persistently normal ALT values when tested serially over a 6-month observation period [6]. A number of studies have been conducted to assess the prevalence, degree and outcome of liver disease in these subjects, after early observations indicating that a subgroup of them may have significant liver damage when evaluated with liver biopsy [7]. The main findings were that significant liver disease, with active inflammation and/or advanced fibrosis, is present in a variable proportion of HCV carriers with normal ALT, with large variations among studies due to different

inclusion criteria and to the baseline follow-up time [8-11]. Indeed, the prevalence of cases with advanced liver disease and/or cirrhosis was significantly higher in studies of HCV carriers with normal ALT who had undergone a liver biopsy after having been tested for ALT for a shorter period or with fewer ALT evaluations, than in those who had been followed for longer periods or with more frequent ALT testing. According to our own recent meta-analysis of published studies [12], 22% of a cumulative 1145 cases with normal ALT had significant liver disease. This figure is consistent with what we have observed recently in our population-based survey showing that significant fibrosis (F2-F3) was detected in 18.7% of HCV carriers with persistently normal ALT [6].

A number of studies have evaluated the short- and long-term outcome in HCV carriers with initially normal ALT [13-15]. All these studies have shown a significant risk of biochemical reactivation, although the frequency varied considerably once again mainly due to different inclusion criteria, number and frequency of ALT evaluation and length of follow-up. In the largest series of HCV carriers published so far, Puoti et al. [10] recently described reactivation of liver damage in 21.5% out of 880 Italian HCV carriers with initially normal ALT levels. Similar findings have been reported by other authors. Interestingly, the probability of having an ALT flare during follow-up was not predictable in most of these studies and did not correlate with initial histologic findings.

Therefore, on the basis of these data it would appear that around 20% of HCV carriers with persistently normal ALT have significant liver disease at liver biopsy and another 20% will develop significant disease reactivation in the medium-term follow-up. However, in other cases the ALT flare is mild and of limited duration and may not affect the overall course of liver disease. Unfortunately, it is difficult to predict at the individual level which patient will show a “clinically significant” ALT flare-up that will affect the progression of liver disease.

“MILD” CHRONIC HEPATITIS C

Chronic hepatitis C is a slowly progressive disease that can be classified as mild, moderate or severe according to liver histology. Most studies indicate that the longer the follow-up, the higher the probability that liver disease will worsen at both the histological and

clinical level in patients who initially presented with histologically mild chronic hepatitis C. This is particularly true in cases with increased ALT levels.

The question of whether liver fibrosis is progressive or not in cases with no or minimal fibrosis (F0/F1) at liver biopsy has recently been addressed in studies where serial liver biopsies were taken during a long-term follow-up in the absence of antiviral treatments. The results of these studies are summarized in Table 1.

Author	**No cases**	**Mean interval between biopsies**	**% with progression of fibrosis**	
			All	Severe fibrosis
Marcellin et al. 2002 [16]	110	3.2 yrs	32%	2%
Ghany et al. 2003 [17]	45	3.8 yrs	42%	4%
Hui et al. 2003 [18]	61	6.3 yrs	33%	10%
Alberti et al. 2004 [19]	105	8.3 yrs	60%	27%

Table 1: Progression of fibrosis in repeated liver biopsies in patients with initial F0/F1

In the report by Marcellin et al. [16], with a shorter follow-up between the initial and final biopsy, (a mean of 3.2 years) only 32% of the patients showed progression of liver fibrosis and only 2% developed severe fibrosis (F3 or F4). Ghany et al. [17] studied 21 patients with no fibrosis and 43 with portal fibrosis on the initial biopsy and reported progression of fibrosis in 13 of the former and in 18 of the latter when followed for a mean period of 3.6 years while untreated. The risk of progression was influenced by the ALT profile, and was significantly higher in patients with initially mild disease and

elevated ALT than in cases with mild disease and persistently normal ALT. Hui et al. [18] described rates of histological progression in 27 patients with F0 (15 with persistently normal ALT and 12 with elevated ALT) and in 34 with F1 (16 with normal ALT and 18 with elevated ALT) in the initial biopsy. These patients underwent a second biopsy after a mean 6.3 (range 2-11.1) years. Progression of fibrosis was seen in 22.5% of cases with normal ALT and in 43% of those with elevated ALT and severe fibrosis developed in 20% of those with elevated ALT. Progression to severe fibrosis or cirrhosis was only seen in patients with F1 in the initial biopsy, while progression in those with F0 was minor. In the group with elevated ALT the cumulative probability of developing severe fibrosis/cirrhosis was estimated to be >50% and >70% 8 years and 10 years respectively after the initial biopsy. In our study [19] in 106 patients with initially mild chronic hepatitis C and with the longest time interval between biopsies in the literature (7-11 years with a mean of 8.3 years) progression of liver fibrosis was seen in 57 cases (60%), including 47 out of 73 (72%) of those with elevated ALT and 10 out of 33 (33%) of those with persistently normal ALT during follow-up. Progression of fibrosis was seen in 6/21 of those with F0 and in 51/85 of those with F1. The corresponding figures for patients with normal and elevated ALT were: normal ALT/F0: 4/18 (22%) with progression of fibrosis; normal ALT/F1: 6/15 (40%); high ALT/F0 2/3 (66%); high ALT/F1: 45/70 (22%). Severe fibrosis only developed in patients with F1 in the initial biopsy and elevated ALT: 12/70 (17%). The mean index of the progression of fibrosis was 0.02/year in those with F0 and normal ALT, 0.11/year in those with F1 and normal ALT, 0.15/year in those with F0 and high ALT and 0.16 in those with F1 and high ALT. By multivariate analysis, the progression of fibrosis correlated with age at diagnosis (P=0.02), mean ALT levels during follow-up (P=0.001), alcohol intake (P=0.05), necroinflammatory activity (P=0.02) and steatosis (P=0.05) in the initial biopsy, but not with the HCV genotype or HCV RNA serum levels (P=NS). Figure 1 describes the rates of progression to severe fibrosis/cirrhosis derived from individual prospective studies with different time intervals between the initial and final biopsy or from published mathematical modeling. Despite the heterogeneity of these studies in terms of included patients and the presence of cofactors, the results of this analysis suggests that there is a significant time-related risk of progression to cirrhosis in patients with F1 in the initial biopsy and abnormal ALT. The corresponding

figures for patients with F0 in the initial biopsy and elevated ALT are much lower, with an estimated incidence of severe fibrosis/cirrhosis <2% at 10 years, <5% at 20 years and <20% at 30 years of follow-up.

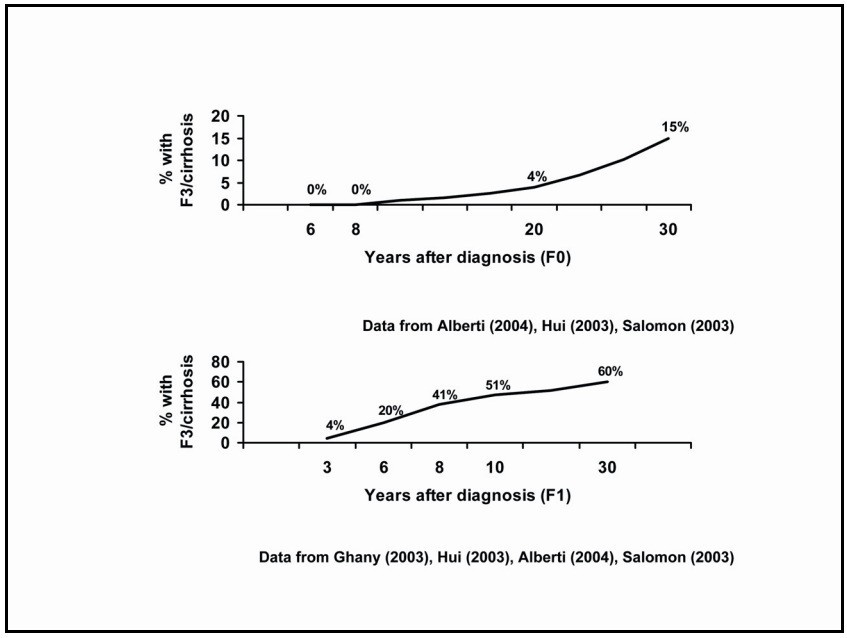

Figure 1: Observed or predicted risk of developing cirrhosis in patients with elevated ALT, according to the initial fibrosis score (F0 or F1).

On the basis of these findings, it is clear that liver disease is progressive in most cases with initially mild chronic hepatitis C in the presence of abnormal ALT levels. According to the available data, more than 50% of patients with F0/F1 in the initial biopsy are expected to progress to more advanced fibrosis (F2/F3) within 5 to 10 years and may develop cirrhosis within 15 to 20 years. Fibrosis may progress even faster in older patients and in the presence of cofactors such as alcohol intake or metabolic abnormalities leading to the accumulation of steatosis in the liver.

The role of cofactors has been clearly demonstrated in recent studies [20-23] and many of the most influential factors such as hepatic steatosis, obesity and moderate alcohol intake, are quite common in the general population and in asymptomatic HCV carriers. Since many studies on the natural course and outcome of initially mild chronic hepatitis C were conducted in selected subgroups of patients, often with exclusion of patients with cofactors that could affect the course of liver disease, these studies could easily have underestimated the risk and speed of the progression of liver disease that may occur in most HCV carriers in the general population, particularly in areas where obesity, metabolic liver steatosis and alcohol consumption are common. Age has been shown to affect the histological progression of chronic hepatitis C, and this is also true for initially mild disease. In our own study [19] conducted in 106 patients with initially mild chronic hepatitis C, the risk of the progression of fibrosis increased by a factor of 1.91 for every 10 years of age, after adjustment for other confounding variables. Thus, age alone appears to directly affect the pathogenicity of HCV. In addition, the progression of liver disease can be further accelerated by increasing age due to the increasing prevalence of metabolic cofactors. Thus, lifetime progression to cirrhosis and to its complications may also occur in middle aged or older patients presenting with histologically mild disease

OUTCOMES IN MODERATE-SEVERE CHRONIC HEPATITIS C

Symptomatic patients with HCV and those with more advanced liver inflammation and fibrosis are at a high risk of progressing to cirrhosis within a relatively short (5-10 years) period of time if left untreated. In mild chronic hepatitis C, a number of cofactors have been shown to influence the rate of progression to cirrhosis. A list of the major cofactors that accelerate the worsening of liver disease are provided in Table 2.

Age at diagnosis
Alcohol intake
Immunogenetics
Iron overload
Liver steatosis
HIV co-infection
HBV co-infection

Table 2: Co-factors shown to influence the rate of progression to cirrhosis in chronic hepatitis C.

NATURAL HISTORY OF HCV-RELATED COMPENSATED CIRRHOSIS

Patients with HCV-related, compensated cirrhosis may remain asymptomatic for many years, and have a normal quality of life. However, recent prospective studies indicate significant morbidity and mortality within the first decade after diagnosis and show that hepatocellular carcinoma is the most frequent and life-threatening complication of initially compensated HCV-positive cirrhosis. We recently described the long-term clinical outcome in a cohort of 269 patients with HCV-related cirrhosis followed prospectively for a mean period of 93 months (range 14-194 months) [24]. During this observation period, 33% developed at least one complication, most frequently and the first to occur being hepatocellular carcinoma. The cumulative incidences of HCC at 5 and 10 years were 7.8% and 28% in patients with HCV alone and 13% and 50% in those with HCV/HBV co-infection. The corresponding cumulative incidences of other complications are described in Table 3.

	Cumulative incidence (%)			
	HCV		HCV/HBV	
Complication	**5 yrs**	**10 yrs**	**5 yrs**	**10 yrs**
HCC	7.8	28	13	50
Ascites	7	20	11	40
GI bleeding	2.5	5	0	5
Encephalopathy	0	2.5	0	5
Liver-related death	5	19	9	8

Table 3: Cumulative incidence of major complications in initially compensated HCV-related cirrhosis.

In this study, as well as in other similar series, the prognosis of HCV-related cirrhosis was worsened by alcohol abuse and HBV co-infection and improved by antiviral therapy.

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