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Hepatitis C Virus II

Infection and Disease

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Part I
Chronic Hepatitis C

Natural History of Chronic Hepatitis C

Marc G. Ghany and T. Jake Liang

Abstract Globally it is estimated there are 200 million persons with chronic hepatitis C virus infection. The infection becomes persistent in 50–80 % of persons who are exposed to hepatitis C virus. Chronic infection with hepatitis C virus is a major cause of cirrhosis, end-stage liver disease and hepatocellular carcinoma. The prognosis of chronic hepatitis C is highly variable and many host, viral and environment factors influence outcome. Approximately 25 % of persons with chronic hepatitis C will progress to cirrhosis over a 25–30 year period and be at risk for complications of end-stage liver disease and hepatocellular carcinoma. Modeling data predicts that the number of individuals with cirrhosis is expected to double by 2030. Many of these individuals will be at risk for end-stage liver disease and hepatocellular carcinoma. Could substantially reduce risk of cirrhosis, decompensation, cancer, and liver-related deaths.

Keywords Hepatitis C virus • Chronic hepatitis C • Natural history • Outcome • Cirrhosis • Decompensated liver disease • Hepatocellular carcinoma

1 Introduction

The natural history of a disease refers to a description of the uninterrupted progression of a disease in an individual from the moment of exposure to causal agents until recovery or death (Bhopal 2002). Defining the natural history of chronic hepatitis C has been difficult for several reasons: the majority of cases of acute hepatitis C are asymptomatic, so identifying cases has proven challenging. By the time they present for medical attention, most subjects have usually progressed to chronic hepatitis. Establishing the duration of disease based on time of exposure is notoriously inaccurate because most individuals cannot recall the date of exposure unless it was due to receipt of a single blood transfusion or accidental needlestick.

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Another problem is the duration required to follow patients for the outcomes of the infection. This usually means decades of follow-up generally exceeding the careers of most researchers. Nevertheless, a fairly comprehensive understanding of the natural history of chronic hepatitis C has been pieced together from prospective and retrospective studies of untreated subjects. What has emerged from this data is the remarkably variable outcome of infection and the large number of factors that seem to influence its outcome. This review will provide a summary of over 30 years of work that has been carried out by many investigators to understand the natural history of chronic hepatitis C.

2 Outcome of Acute Hepatitis C

2.1 Clinical Course

Acute hepatitis C usually presents without symptoms and the majority of persons are unaware of the infection. Approximately 15–30 % are symptomatic and variably report fatigue, lethargy, myalgia and loss of appetite. Fewer than 1 % of cases present with jaundice. Hepatitis C virus (HCV) RNA is usually detectable within 2 weeks after infection and HCV specific antibody within 12 weeks of exposure. Serum alanine aminotransferase (ALT) levels usually rise within 8–10 weeks with the peak ALT ranging from 10 to 20 times the upper limit of normal. Interestingly, as the disease progresses, serum HCV RNA levels may be observed to fluctuate and even become negative only to reappear again. This finding is characteristic of the acute but not chronic phase of the infection and may be a clue to the diagnosis of acute infection.

Follow-up studies from cohorts with acute hepatitis C in which the time of exposure could be established with some precision, such as cases of post-transfusion hepatitis or injection drug users who were prospectively monitored with serial HCV RNA determinations, indicated that approximately 15–25 % of patients with acute hepatitis C spontaneously resolve their infection (Gerlach et al. 2003; Deterding et al. 2013; Villano et al. 1999; Tremolada et al. 1992). Rates of spontaneous resolution of acute hepatitis C may be higher, 45–50 %, in certain populations for example subjects who present with jaundice compared to asymptomatic individuals, (Gerlach et al. 2003) in persons who are infected at younger compared to older age (age >40 years) (Vogt et al. 1999) and among women compared to men (Kenny-Walsh 1999; Wiese et al. 2000). More recently, certain polymorphisms (the rs12979860-C, (Ge et al. 2009) rs8099917-T (Tanaka et al. 2009) and the ss469415590 TT (Prokunina-Olsson et al. 2013) variants), near to the IL28B gene that encodes for lambda interferon – a type III interferon – were shown to be associated with higher rates of spontaneous clearance of HCV infection. Viral factors also appear to affect resolution of infection and persons with

recovery from acute hepatitis C were found to have less genetic diversity of the virus compared to those who progressed to chronic infection (Farci et al. 2000).

3 Outcome of Chronic Infection

Persons who fail to clear virus after a period of 6 months are generally accepted to have chronic infection, but viral clearance may occur well beyond 6 months in many infected individuals. Some, but not all of individuals with chronic infection are at risk for progressive liver disease including cirrhosis, decompensated liver disease, hepatocellular carcinoma and death (Fig. 1). The ideal natural history study would follow a large cohort of both men and women with known date of infection and who remained untreated throughout their course until death. For obvious reasons, such a study would be very difficult to conduct. So investigators have had to resort to other approaches to define the natural history of HCV infection. Three approaches have been taken, retrospective, prospective and retrospective-prospective cohort studies.

3.1 Retrospective Studies

Retrospective studies identified subjects with chronic hepatitis C and compared the severity of liver disease based on liver histology or clinical features with the time of exposure based upon receipt of blood products or first use of injection drugs (Table 1). These studies were influenced by selection bias, in that most were conducted in tertiary medical centers where patients with presumably more advanced disease were disproportionately represented since they were more likely

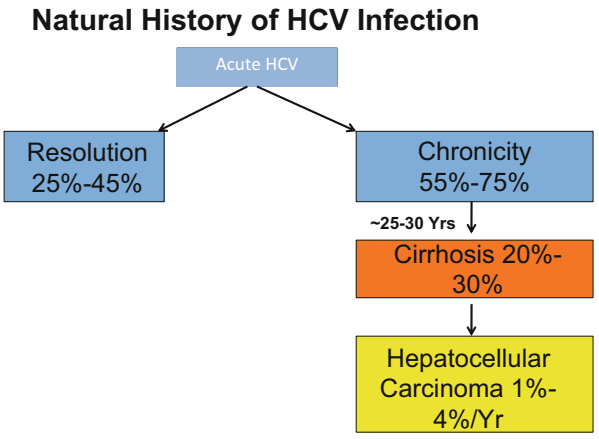

Fig. 1 Natural history of HCV infection

Table 1 Retrospective studies

Author	No.	Mean age	Mode of transmission	Duration of F/U (years)	Prevalence of cirrhosis	HCC	Liver related death/LT
Kiyosawa	231		PTH	10–29	35	23	
Tong	131	57	PTH	1–15	51	5	
Niederau	838		Mixed	9–16	17		
Gordon	627		Mixed	1–25	37	4	9
Gordon	140	58/38	PTH/IDU	13/16	66/33		
Ferenci	485	22[a]	PTH	31	34	5	13
Franchini	102	45	PTH	15–34	7	2	3
Forns	116		Multiple/ Unk	21–27	39	7	6
Posthouwer	212	1.8[a]/ 21		11–28	5[b]		

PTH post-transfusion hepatitis, *IDU* Injection drug use, *Unk* unknown
[a]Mean age at transfusion
[b]All cases HIV-HCV co-infected

to present for medical attention and are also affected by recall bias regarding the time of exposure. These retrospective studies presented a rather grim view of chronic hepatitis C. Cirrhosis was reported to be present in 14–55 % of subjects with chronic hepatitis C after average an disease duration of 1–34 years (Tong et al. 1995; Kiyosawa et al. 1990; Gordon et al. 1993, 1998; Niederau et al. 1998; Ferenci et al. 2007; Franchini et al. 2001; Forns et al. 2001; Posthouwer et al. 2006). Moreover, 2–23 % had developed hepatocellular carcinoma (HCC) and mortality from liver disease was 3–13 % (Tong et al. 1995; Kiyosawa et al. 1990; Gordon et al. 1993, 1998; Niederau et al. 1998; Ferenci et al. 2007; Franchini et al. 2001; Forns et al. 2001; Posthouwer et al. 2006). In one notable study, 131 subjects with transfusion acquired chronic hepatitis C were identified at a tertiary medical center in the Unites States. At initial evaluation 44 % had chronic hepatitis, 50 % had cirrhosis and 5 % had HCC, a mean of 22 years after transfusion. There was a clear trend for worse outcomes with longer duration of disease (Tong et al. 1995). The mean time from transfusion to diagnosis of cirrhosis was 21 years and for HCC, 28 years.

3.2 Prospective Studies

Prospective studies identified subjects with acute hepatitis C with known date of exposure and followed patients over time for development of outcomes. Several prospective studies of patients with transfusion and community acquired hepatitis C have been conducted (Table 2). The major limitations of these studies have been the relatively short period of follow-up ranging from 2 to 16 years and not all subjects

Table 2 Prospective studies

Author	No.	Mean age (years)	Mode of transmission	Duration of F/U (years)	Incidence of cirrhosis	HCC	Liver related death
Realdi	21	48	PTH	2–5	24		5
Tremolada	135	54	PTH	7.5	32	1	
DiBisceglie	65	52	PTH	9.7	20		6
Mattsson	61		PTH	13	8		1.6
Koretz	90	52	PTH	16	11		2
Thomas	1,667	34	IDU	14	1		2

underwent evaluation including liver biopsy. Another bias was that subjects were mostly middle-aged at time of exposure to HCV with an average age at transfusion that ranged between 48 and 54 years and were more likely to have underlying co-morbid conditions that could affect outcome of hepatitis C. Collectively, these studies reported incidence rates of cirrhosis of 8–32 % and liver-related death from 2 to 6 % over 2–16 years (Di Bisceglie et al. 1991; Tremolada et al. 1992; Mattsson et al. 1993; Koretz et al. 1993; Realdi et al. 1982; Thomas et al. 2000a). In studies that reported on the development of HCC, the rate was 0–1.3 %. In one study, subjects who contracted hepatitis C as a result of transfusions administered during cardiac surgery were prospectively followed for development of outcomes. Among 1,070 transfused patients, 65 (6.1 %) developed post-transfusion hepatitis, in whom 45 (69 %) the infection became chronic (Di Bisceglie et al. 1991). Thirty-nine subjects were followed for a mean of 9.7 years (range 1–24 years). During this period, cirrhosis developed in 20 % of subjects and 12 % developed decompensated liver disease (Di Bisceglie et al. 1991). In another study from Italy, outcomes were reported on 135 cases of post-transfusion hepatitis C, most cases following cardiac surgery (Tremolada et al. 1992). Spontaneous resolution was observed in 31 (23 %) cases while chronic hepatitis developed in 104 (77 %). After a mean follow-up of 90 months (range 13–180), cirrhosis was observed in 21 of 65 (32 %) of subjects who underwent one or more liver biopsies, 3 of 104 (3 %) developed end-stage liver disease and 1 (1 %) developed HCC (Tremolada et al. 1992). Thus, the prospective studies of subjects with post-transfusion hepatitis C also suggested high rates of development of cirrhosis but low rates of end-stage liver disease and HCC presumably due to the relatively short duration of follow-up.

3.3 Retrospective-Prospective Studies

Many studies have delineated the outcome of chronic hepatitis C based on identification of subjects who acquired hepatitis C in the past and were re-investigated and prospectively followed to determine the incidence of spontaneous clearance, cirrhosis, end stage liver disease, HCC and liver-related death. These studies have included a broad spectrum of populations infected with hepatitis C through multiple