MEDICAL REVIEW

Natural History of Hepatitis C Infection: A Concise Review

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INTRODUCTION

Chronic hepatitis C virus (HCV)\(^b\) infection is a major public health problem, affecting over 2.7 million individuals in the U.S. and over 170 million worldwide [1, 2]. In the United States, HCV infection is the most common cause of chronic liver disease, accounts for 8,000 to 10,000 deaths annually, and is the leading indication for liver transplantation [3]. Since the initial discovery of HCV virus as the causative agent of non-A, non-B (NANB) hepatitis by Choo and colleagues in 1989 [4], significant advances have been made in our understanding of its epidemiology, pathogenesis, diagnosis, and therapy. Increased understanding of the natural history of chronic infection will be essential in any effort to further elucidate pathogenetic mechanisms, predict clinical outcomes, and identify those patients for whom treatment is beneficial.

Acute infection with HCV virus is usually asymptomatic, and therefore infrequently diagnosed during this early period. Although up to one-third of patients may develop mild flu-like symptoms or jaundice, fulminant liver failure is very rare [5]. Despite vigorous humoral and cell-mediated immune responses by the host, approximately 85 percent of patients fail to achieve spontaneous recovery and thus develop chronic infection, defined as a positive HCV antibody and RNA at six months. Chronic infection is typically characterized by a prolonged asymptomatic period, but will eventually lead to chronic hepatitis, cirrhosis, and hepatocellular carcinoma in 70 percent, 20 percent, and 4 percent of cases, respectively [6].

Mechanisms for HCV persistence remain unclear, but may involve viral mutation during replication, persistence in extrahepatic tissues, or formation of quasispecies that escape host immune response [7-8].

The natural history of HCV infection has been difficult to study. Accurate determination requires a well-defined time of disease onset and frequent, prospective monitoring of clinico-pathologic outcomes over the course of infection without therapeutic intervention, ideally with a matched control group for comparison.

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\(^{b}\) Abbreviations: ALT, alanine aminotransferase; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; HVR1, hypervariable region 1; NANB, non-A, non-B.
This has been limited by several factors: 1) the time of infection onset or acute hepatitis is rarely identified; 2) chronic infection is usually asymptomatic; 3) the development of measurable endpoints may require several decades; 4) highly variable frequency and timing of liver biopsies may delay diagnosis of cirrhosis until clinically evident; and 5) many patients with HCV infection have been exposed to antiviral therapy. Nevertheless, a number of studies conducted in the past ten years have contributed important information about clinical outcomes in chronic hepatitis C infection. Approaches used to study natural history have included prospective studies that follow patients forward from time of disease onset (i.e., post-transfusion hepatitis), retrospective studies that evaluate patients with established clinical outcomes of HCV infection, and nonconcurrent prospective studies that follow cohorts with historically defined times of disease onset (i.e., recognized outbreaks of acute hepatitis).

**RETROSPECTIVE STUDIES**

Current literature from retrospective studies predicts that approximately 20 percent of patients with chronic hepatitis C will develop cirrhosis by twenty years of infection [9], in whom a subset will progress to decompensated hepatic failure and hepatoma. Four retrospective studies have investigated the rate of development of clinical outcomes in patients with established chronic hepatitis, by tracing the chronic disease back to an estimated time of disease onset [10-13]. While obviating the need for a prolonged follow-up period, these studies are limited by inherent uncertainties in time of disease onset, a systematic exclusion of infected patients who never seek medical attention due to spontaneous recovery or lack of symptoms, and a disproportionate inclusion of patients with particularly severe disease.

In 1990, Kiyosawa and colleagues [10] described their results of a retrospective analysis of 231 patients with chronic NANB hepatitis, in whom liver-related complications were identified (96 patients with chronic hepatitis, 81 patients with cirrhosis, and 29 patients with HCC). The authors hypothesized that reliable information on duration of infection could be obtained only from those patients with an accurate time of disease onset (i.e., history of transfusion). Within each complication group, patients with a history of transfusion were identified and points of infection determined. In this highly selected group of patients with advanced disease, the mean time interval between transfusion and cirrhosis was approximately 21 years (Table 1). Their observation provided the earliest evidence that progression to serious clinical outcomes was a gradual process that occurred over decades.

Tong and colleagues [11] corroborated these findings in their study of 213 patients with transfusion-related chronic HCV infection, who were referred to their tertiary care center because of: 1) alanine aminotransferase (ALT) abnormalities; 2) established liver disease; or 3) liver mass. Liver biopsies were performed in 101 of these patients, in whom alarmingly high rates of complications occurred. Based on the time of transfusion, intervals from onset of infection to liver-related outcomes were calculated (Table 1). A smaller group of patients (131) in this study were followed for an additional 3.9 years (mean), during which seven more patients (5.3 percent) developed HCC and twenty patients (15.3 percent) died from liver-related complications. These impressive numbers clearly demonstrated the potential for life-threatening outcomes in chronic HCV infection, but likely grossly overestimated its frequency due to severe referral bias.

Yano and colleagues [12] evaluated the rate of histologic disease progression in a cohort of 80 patients with HCV-related
Table 1. Rate of progression of chronic HCV infection in retrospective studies.

| Author        | Country | No. of patients | Mean interval (years) | Mean interval (years) | Mean interval (years) |
|---------------|---------|----------------|-----------------------|-----------------------|-----------------------|
| Kiyosawa [10] | Japan   | 231            | 10.0 ± 11.3           | 21.2 ± 9.6            | 29.0 ± 13.2           |
| Tong [11]     | USA     | 213            | 13.7 ± 10.9           | 20.6 ± 10.1           | 28.3 ± 11.5           |

chronic liver disease (out of 2,000 eligible participants) who underwent repeated liver biopsies (mean 3.9) over a period of 2 to 26 years. Using a standardized system of histopathology scoring for inflammation and fibrosis, the authors were the first to observe that the rate of progression to cirrhosis was accelerated in patients whose initial biopsies demonstrated high grades of necroinflammatory activity and evidence of hepatic fibrosis. Several years later, Gordon and colleagues [13] examined the relationship between route of infection and clinical outcome in a group of 627 nonalcoholic patients with chronic HCV infection. Biopsy-demonstrated cirrhosis was found in 118 of 215 patients (55 percent) with transfusion-related infection, in contrast to only 40 of 195 patients (21 percent) who transmitted infection through other parenteral routes. HCC also developed more commonly in the group with a history of transfusion (4 percent versus 1 percent). The authors’ findings suggested that the risk of progressive liver failure in hepatitis C infection may correlate with mode of infection, and not duration of infection alone.

PROSPECTIVE STUDIES

Five studies have followed patients prospectively from the time of disease onset to histologically defined outcomes [14-18], all in the setting of transfusion-associated NANB hepatitis. As expected, the inclusion of a wider spectrum of both healthy and symptomatic patients has resulted in numbers suggesting a lower rate of progression to end-stage liver disease (Table 2). These authors demonstrate that the development of complications is highly variable, but appears to be benign in most patients during the first decade of infection. These studies are limited, however, by the absence of controls, the intro-

Table 2. Prospective long-term outcomes in patients with transfusion-associated NANB hepatitis.

| Author       | Country | No. of patients | Mean follow-up (years) | Cirrhosis (Percent) |
|--------------|---------|----------------|------------------------|---------------------|
| Hopf [14]    | Germany | 86             | 8.0                    | 24.0                |
| DiBisceglie [15] | USA   | 65             | 9.7                    | 12.3                |
| Tremolada [16] | Italy | 135            | 7.6                    | 15.6                |
| Koretz [17]  | USA     | 80             | 14.0                   | 6.3                 |
| Mattson [18] | Sweden  | 61             | 13.0                   | 8.0                 |
duction of disease-modifying treatments, and short surveillance duration (range 7.6 to 14.0 years) that is clearly inadequate to capture the full range of hepatitis C-related complications.

The study boasting the longest duration of follow-up, conducted by Koretz and colleagues [17], illustrates these limitations well. Following documented acute transfusion-associated NANB hepatitis in 90 patients, 80 were followed for approximately 16 years following transmission, in whom 55 patients (69 percent) developed chronic hepatitis C infection. Only eight patients in this cohort prospectively underwent liver biopsy, of whom three demonstrated cirrhosis. An additional two patients were reported to have documented cirrhosis on earlier biopsies. Thus despite a reassuring figure of 6.3 percent cirrhosis at a mean of 14.0 years, the absence of more biopsy data prevents one from reaching broader conclusions regarding long-term outcomes. Notably, decompensated liver disease was estimated to be present in 19 percent of all patients in this cohort, reflecting the true possibility of under-diagnosis.

Several investigators have studied the progression of disease beginning in patients who already have established chronic hepatitis. Poynard and colleagues [19] have long described the course of chronic hepatitis C infection in terms of progression from chronic inflammation to fibrosis to cirrhosis. Fibrosis stage and disease activity, as measured by standardized histologic criteria (i.e., METAVIR scoring system), may serve as valuable surrogate markers for disease progression. In this study, liver biopsies of 2,235 patients were obtained from three large population-based study groups, and reviewed singly or in paired samples. Defining fibrosis progression as a ratio between fibrosis stage (in METAVIR units) and estimated duration of infection (in years), the authors reported a median rate of fibrosis progression of 0.133 fibrosis units per year, which is independently increased by advanced age (greater than 40 years old at time of infection), daily alcohol consumption (greater than 50 g/day), and male sex. They further concluded that the median estimated interval between infection and cirrhosis is 30 years, ranging between 13 years (in male alcoholics over age 40) and 42 years (in non-drinking females infected before age 40). This distribution suggests the presence of at least three populations: 1) "rapid fibrosers" (progress to cirrhosis in 5 to 10 years), 2) "intermediate fibrosers" (cirrhosis in 11 to 30 years), and 3) "slow fibrosers" (cirrhosis in greater than 30 years or not at all).

NONCONCURRENT PROSPECTIVE STUDIES

During the past five years, the scientific community has witnessed an explosion of studies that identified for prospective evaluation a historically defined cohort of patients with a clearly recognized point of infection, usually in the setting of an acute outbreak of NANB or type C hepatitis (Table 3) [20-27]. In nearly all cases, the rate of progression to cirrhosis at twenty or more years is significantly less than suggested by retrospective study literature. This supports the growing notion among practicing hepatologists that the natural history of chronic hepatitis C infection is heterogeneous, and likely more benign that previously believed.

Kenny-Walsh and the Irish Hepatology Research Group [20] described a long-term follow-up study of 704 women who received HCV-contaminated anti-D immune globulin in 1977, and were found to be anti-HCV positive 17 years later in 1994. Liver function tests were normal in 45 percent of women. Of 363 women who underwent liver biopsies, the vast majority demonstrated mild or moderate necroinflammatory changes (93
percent) and portal or periportal fibrosis was seen in 34 percent of patients. Notably, however, fibrosis was absent in nearly one-half of patients (49 percent) and cirrhosis was found in only 2 percent of patients. Muller [22] reported nearly identical results in 152 German women who received contaminated Rh immune globulin, noting that not a single patient demonstrated cirrhosis at 15 years of follow-up. Similarly encouraging results were reported by Wiese and colleagues [25] from their evaluation of 917 East German women who transmitted HCV infection from contaminated immune globulin. Nearly 85 percent of these patients remained anti-HCV positive at 20 years, only 55 percent remained HCV RNA positive, and cirrhosis was detected in only four patients (0.4 percent), two of whom were co-infected with hepatitis B virus.

The surprisingly benign clinical outcome observed in these patients may reflect, in part, a very low-risk population of young, otherwise healthy, non-drinking women. It is uncertain if similar results would be found in other populations. Yet similar results were reported in long-term follow-up studies of stored sera from healthy young American military recruits [23] and follow-up of healthy young German adults with prior transfusion-associated hepatitis [27], suggesting that hepatitis C infection is likely associated with few, if any long-term complications in low-risk individuals.

More recently, Thomas and colleagues [28] prospectively evaluated the incidence and predictors of viral clearance and advanced liver disease in a community-based cohort of 919 patients who acquired HCV infection in the context of injection drug use. The authors recognized that injection drug use accounts for 60 percent of all new cases in the U.S. [29], and that prior studies did not adequately evaluate clinical outcomes in this population, focusing instead on older transfusion-infected patients with multiple co-morbidities, or young, healthy immune globulin recipients. The authors found that after a median of 13.7 years of drug use and 8.8 years of follow-up, viral clearance occurred more frequently in nonblacks (OR 5.15) and that the risk for clinically evident end-stage liver disease was higher in patients who were over 38 years old (OR 3.67) or drank >260g alcohol/week (OR 3.60). Of 210 patients who underwent liver biopsy, only two (1 percent) demonstrated cirrhosis. Drawing conclusions from this study are limited by its use of a proxy time of infection (onset of infection

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**Table 3. Nonconcurrent prospective outcomes in patients with historically defined points of infection.**

| Author            | Country    | No. of patients | Mean follow-up (years) | Cirrhosis (Percent) | Year Published |
|-------------------|------------|-----------------|------------------------|---------------------|----------------|
| Kenny-Walsh [20]  | Ireland    | 376             | 17                     | 2.0                 | 1999           |
| Wright [21]       | USA        | 568             | 23                     | 15.0                | 1998           |
| Muller [22]       | Germany    | 152             | 15                     | 0.0                 | 1996           |
| Seeff [23]        | USA        | 17              | 50                     | 0.06                | 2000           |
| Gronbaek [24]     | Denmark    | 178             | 23                     | 9.0                 | 1999           |
| Wiese [25]        | Germany    | 917             | 20                     | 0.4                 | 2000           |
| Rodger [26]       | Australia  | 238             | 25                     | 8.0                 | 2000           |
| Vogt [27]         | Germany    | 458             | 20                     | 0.002               | 1999           |


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defined as first reported injection drug use), an inadequate duration of follow-up to observe clinical end-points, and the use of clinical definitions for end-stage liver disease, clearly a less sensitive marker that biopsy in detecting cirrhosis.

**FACTORS THAT MAY PROMOTE DISEASE PROGRESSION**

From the available literature of the past three years, it is clear that cirrhosis and its life-threatening complications are not inevitable in all patients with hepatitis C infection. Many viral, environmental, and host factors may dramatically affect the likelihood of promoting disease progression. Age at time of infection, male gender, alcohol consumption, HIV co-infection, low CD4 count, and HBV co-infection have been clearly demonstrated to accelerate fibrosis progression rate. Viral factors such as viral load (RNA), genotype, and quasispecies formation have not been shown to be associated with fibrosis progression.

The effect of alcohol on fibrosis acceleration in patients with HCV infection is substantial even in moderate amounts; abstinence should be encouraged in most patients. Excessive amounts greater than 40 g/day in women and 60 g/day in men dramatically and independently increase the risk of cirrhosis [30-31]. The mechanism remains unclear, but may involve altered host immune response to viral infection. Advanced age increases fibrosis progression significantly through heightened vulnerability to oxidative stress and diminished immune capacity. Statistical modeling has demonstrated that the probability of disease progression in men aged 61 to 70 was 300 times greater than for men aged between 21 to 40, highlighting its important place clinical decision-making [32]. Females have been found to have a ten-fold decreased progression rate than men at all ages, possible related to estrogen-mediated modulation of fibrogenesis [33].

Co-infection with HIV is associated with accelerated fibrosis progression, particularly in those patients with low CD4 counts (<200 cells/ul) or concurrently drink alcohol [34]. Both of these risk factors accelerated the median expected time to cirrhosis to 16 years from 36 years in controls.

Co-infection with hepatitis B infection accelerates fibrosis and increases the risk of cirrhosis complicated by hepatocellular carcinoma [35]. Hepatitis A co-infection is usually self-contained but may increase the risk for developing fulminant hepatitis and hepatic failure [36]. Vaccination against hepatitis A and B should be performed routinely in previously unimmunized patients.

Although helpful in predicting response to interferon-based therapy, hepatitis C RNA and genotype do not correlate with progression of disease [37-38]. The formation of distinct but closely related viral mutants (quasispecies) within individual patients was previously believed to be unrelated to severity of HCV-related liver disease. However, a recent investigation by Farci and colleagues suggests that examination of the genetic diversity of the virus during the first four months of infection may predict whether HCV infection will become chronic or resolve spontaneously [8]. The authors detected a marked increase in the genetic diversity of the hypervariable region 1 (HVR1) of the virus in patients with hepatitis C proved to be progressive. Conversely, patients whose infection eventually resolved demonstrated a decrease in genetic diversity of HVR1, as manifested by the mean number of non-synonymous nucleotide substitutions per week. This raises the possibility that different modes of HCV transmission may result in critical differences in quasispecies generation and genetic diversity,
thereby resulting in disparate clinical outcomes.

CONCLUSIONS

Chronic HCV infection remains a critical public health priority. Future morbidity, mortality, and cost resulting from hepatitis C-related care is expected to be astronomical, with a predicted 165,900 deaths from chronic liver disease, 27,200 deaths from hepatocellular carcinoma, and $10.7 billion in direct medical expenditures between 2010-2019 [39]. Based on current literature, we can safely predict that most patients with hepatitis C infection will develop chronic hepatitis, and that many of these patients will progress at variable rates toward cirrhosis and its complications. In midst of rapidly advancing therapies [40] and prospects of exciting new research animal models [41], our facility in helping patients determine their individual risks for disease progression and suitability for treatment will be essential.

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