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REVIEW ARTICLE

Natural history of HCV infection

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Abstract
Background There is much controversy surrounding the natural history of hepatitis C virus (HCV) infection.
Aims The aim of this review was to review the natural history of HCV infection.
Methods Published English literature was searched via pubmed and then reviewed.
Results Approximately, 75–85% of HCV-infected persons will progress to chronic HCV infection. The rate of chronic HCV infection is affected by a person's age, gender, race, and viral immune response. Once chronic HCV infection develops, there are external and host factors that can increase the risk of progression of liver disease. Progression of chronic HCV infection is not linear in time, probably because many cofactors change the rate of development of fibrosis, cirrhosis, and hepatocellular carcinoma. Factors linked with aggressive disease progression include age at infection, duration of infection, heavy alcohol use, co-infections with HIV or hepatitis B virus, male sex, steatosis, insulin resistance (and factors associated with the metabolic syndrome), and host genetics. However, the relative importance of many and varied factors remains uncertain, and further research efforts should be directed toward design of predictive models for effective risk stratification. Interferon-based therapy, particularly among those achieving a sustained virologic response (SVR), is associated with improved fibrosis and inflammation scores, reduced incidence of hepatocellular carcinoma, and prolonged life expectancy.
Conclusions Despite the progress in understanding the factors affecting the natural history of HCV infection, a great deal remains to be learnt.

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Introduction

The natural history of hepatitis C is quite varied. There are some inherent drawbacks in studying natural history. First, it is difficult to ascertain the exact time of acquirement of infection; second, primary infection is commonly asymptomatic and last, disease progression is slow. Natural history data reported in the literature vary according to the type of study (retrospective vs. prospective). Different study populations also result in different predictions about natural history (patients attending liver clinic vs. blood donors vs. community-based studies vs. post-transfusion cohorts).

Acute hepatitis C virus infection

Acute hepatitis C virus (HCV) infection is infrequently diagnosed, because the majority of acutely infected individuals are asymptomatic. In the transfusion setting, where acute onset of HCV infection has been best documented, 70–80% of cases were asymptomatic. About 20–30% of adults with acute HCV infection may develop clinical symptoms.

The onset of symptoms occurs from 3 to 12 weeks after exposure. Symptoms may include malaise, weakness, anorexia, and jaundice. Elevation of serum alanine aminotransferase (ALT) levels occurs 2–8 weeks after exposure and often reaches levels of greater than ten times the upper limits of normal.

HCV RNA can be detected in the serum within 1–2 weeks after exposure. The level of HCV RNA rises rapidly during the first few weeks and then peaks between

10^5 and 10^7 IU/mL, shortly before the peak of serum aminotransferase levels and onset of symptoms [1].

In self-limited acute HCV infection, symptoms can last several weeks and subside as ALT and HCV RNA levels decline. The fluctuating nature of the infection can be seen in 10–15% of the subjects with marked variation in levels of ALT and aspartate aminotransferase (AST) in association with marked changes in HCV RNA levels including periods of HCV RNA negativity followed by reappearance of HCV RNA. In most patients, fluctuations are present only during the first 24 weeks after exposure; however, these may continue beyond 24 weeks [2].

The antibody to HCV, as detected by enzyme immunoassay, becomes positive at the onset of symptoms, approximately 1–3 months after exposure. Up to 30% of patients will test negative for anti-HCV at onset of their symptoms, making anti-HCV testing unreliable in diagnosis of acute infection. Almost all patients eventually develop the antibody to HCV; however, titers can be low or undetectable in immunodeficient patients. The anti-HCV assay detects >90% of HCV infections after the initial 3 months.

Acute HCV infection can be severe, but fulminant liver failure is rare [3, 4]. HCV RNA clearance estimates in longitudinal studies have been reported in the range of 0–57%. These studies are heterogeneous in terms of their study populations and the majority is clinic-based acute hepatitis C case series using descriptive methodologies. Findings from sero-incident cohort studies have been more consistent in their findings, reporting clearance rates of between 15 and 20%. The reported estimate of time to clearance has ranged from 1 to 2 weeks up to 1–3 years. Discrepancies in these estimates have been attributed to a number of factors. First, the asymptomatic nature of early infection means that detection of acute infection is uncommon. Second, there are currently no diagnostic tests to differentiate between acute and chronic infection. Third, the majority of HCV infections occur in marginalized population, such as injecting drug users (IDUs), who may be difficult to recruit in studies and maintain in follow-up. Last, the statistical methods and definitions used to determine clearance estimates vary between studies. HCV RNA clearance rate is higher with clearance defined as a single negative HCV RNA result compared to two negative HCV RNA results, which should be the preferred approach in defining RNA clearance [5].

Chronic hepatitis C (CHC) is marked by the persistence of HCV RNA in the blood for at least 6 months after onset of acute infection. Approximately, 80–85% of infected patients do not clear the virus by 6 months.

Risk factors for developing chronic HCV infection

The rate of development of chronic HCV infection is affected by many factors, including the age at the time of infection, gender, ethnicity, and the development of jaundice during the acute infection.

Age

The chronicity rate in HCV infection appears to be lower in younger individuals. In the Dionysos study from Italy, residents between the ages of 12 and 25 years had a chronicity rate of 56%, compared with 87% for those above the age of 25 years [6].

Gender

In retrospective analyses, the rate of chronicity in HCV infection appears to be lower in women, particularly younger women. However, large cross-sectional studies have not demonstrated gender differences in the rate of chronicity in HCV infection.

Ethnicity

African-Americans appear to have a higher rate of chronic HCV infection than Caucasians and Hispanic whites.

Symptomatic acute infection

The rate of chronic HCV infection is lower in patients who develop jaundice or symptoms during the acute onset of HCV infection as compared to those who are anicteric.

Immune responses during acute infection

The rate of chronic HCV infection developing in patients with human immunodeficiency virus (HIV) infection and CD4 <200 has been higher than that in patients without HIV infection [7, 8].

The mechanisms leading to viral eradication are presently not understood, although data support a role for both innate and adaptive immune responses as being required for viral clearance. Disruption of innate immune pathways by structural (core, E2) and non-structural (NS3, NS5A) HCV proteins supports a role for innate immune responses in viral clearance [9]. With regard to the role of the adaptive immune response, vigorous and multispecific CD4+ and CD8+ T-cell responses, which appear in acute infection and persist overtime, have been associated with viral resolution [10]. In addition, depletion studies in chimpanzees confirmed the crucial role of these cells in viral clearance [11].

Chemokines produced in the liver during HCV infection induce migration of activated T cells from the periphery to infected parenchyma. These chemokines consist of CCL3 (macrophage inflammatory protein-1α; MIP-1α), CCL4

(MIP-1β), CCL5 (regulated on activation normal T cell expressed and secreted; RANTES), CXCL10 (interferon-γ – inducible protein-10; IP-10), CXCL11 (interferon-inducible T-cell α chemoattractant; I-TAC), and CXCL9 (monokine induced by interferon γ; Mig) and they recruit T cells expressing either CCR5 or CXCR3 chemokine receptors. The interaction between chemokines and their receptors is essential in recruiting HCV-specific T cells to control the infection. In a resolved infection, HCV-specific cytotoxic T lymphocytes (CTL) migrate rapidly to the infected liver, attracted by the chemokines produced by hepatocytes, succeeding in controlling HCV infection without liver damage. Recently week-to-week oscillations of HCV RNA, chemokines, and ALT have been shown and this suggest frequent, repeated cycles of gain and loss of immune control during acute HCV infection [12]. When the adaptive immune response fails in controlling HCV during the acute stage, non-specific T cells without the capacity to control the infection are also recruited to the liver, and these are ultimately responsible for the persistent hepatic damage.

Host genetic factors

Host genetic variation is assumed to explain the heterogeneity in HCV clearance across individuals because such differences occur even after exposure to the same HCV inoculum and because there are ethnic differences in clearance frequency. Variation in genes involved in the immune response has been linked to the outcome of acute HCV infection, presumably owing to the alteration in the strength and quality of the immune response. Human leukocyte antigen (HLA) class II and some genetic signals located in the 19q13 region, including IL28B, KIR2DL3, TGFb1, LDLR, and APOE, are the strongest predictors of spontaneous clearance [13]. Recent study has found that a single nucleotide polymorphism (rs12979860) 3 kb upstream of the IL28B gene, which encodes the type III interferon IFN-γ3, is the strongest and most significant genetic effect associated with natural clearance of HCV. Patients with the C/C genotype were three times more likely to clear HCV relative to patients with the C/T and T/T genotypes combined [14]. The frequency of HCV clearance varies markedly across ethnic groups, as there are differences in allele frequencies for the rs12979860. The global pattern of allele frequencies shows a striking pattern in which the allele leading to greater natural HCV clearance is nearly fixed throughout East Asia, has an intermediate frequency in Europe, and is the minor allele in Africa [15].

Chronic HCV infection

There have been extensive studies focusing on the natural course of disease progression in CHC, including fibrosis progression and development of cirrhosis and hepatocellular carcinoma (HCC).

Natural progression of liver disease in chronic HCV infection

Published estimates of fibrosis progression and time to cirrhosis are dependent on study design and the patient population investigated. Retrospective studies have often been derived from large tertiary referral centers and may reflect ascertainment bias because individuals with advanced liver disease are more likely to be referred. Even the prospective studies fail to provide information on long-term outcomes. Yet another approach is retrospective–prospective studies in which the precise time at which past infection with acute hepatitis C can be defined retrospectively and the subjects were subsequently followed prospectively. These studies, however, involve mainly cohorts of young females in whom abstinence from alcohol was advised.

In early retrospective studies, intervals from exposure range from 9 to 29 years, development of cirrhosis occurred in 17–55%(mean 42%), HCC developed in 1–23%, and liver-related death occurred in 4–15% of patients. In early prospective studies, intervals from exposure range from 8 to 16 years, development of cirrhosis occurred in 7–16% (mean 11%), HCC developed in 0.7–1.3%, and liver-related death occurred in 1.3–3.7% of patients. In early retrospective–prospective studies, intervals from exposure range from 9 to 50 years, development of cirrhosis occurred in 0.3–15%, HCC developed in 0–1.9%, and liver-related death occurred in 0–2.8% of patients [16]. Cumulatively, these studies do suggest that there is a variable rate of disease progression to cirrhosis and its complications, likely because of multiple factors.

Studies of patients who acquired acute HCV from a blood transfusion generally describe no increase in all-cause mortality if the follow-up is less than 25 years. These observations may reflect that not all patients became chronically infected or developed significant liver disease following acute infection. In contrast, studies of patients who presented with chronic hepatitis tend to report a more aggressive course with a high risk of cirrhosis, decompensation, and HCC. In one series from the United States, e.g., 131 patients with chronic post-transfusion hepatitis C were evaluated a mean of 22 years after transfusion: 23% had chronic active hepatitis, 51% had cirrhosis, and 5% had HCC [17]. The HCC developed in an additional seven patients, an average of 36 months, after the initial visit. It was estimated that the mean duration of infection among patients who developed cirrhosis was 20.6 years. Similar data were observed in studies from Japan and France [18].

Development of cirrhosis and its complications

The progression to cirrhosis is often clinically silent, and some patients are not known to have HCV until they present with the complications of end-stage liver disease. Cirrhosis rates become significant after 20 years of infection.

The time from HCV infection to cirrhosis is dependent on multiple factors and cannot be predicted in an individual patient. Multiple studies have attempted to measure the time interval from infection to cirrhosis and HCC. Frequently, the initial time of infection is not known and, therefore, must be estimated. On the other hand, individuals who contracted HCV through a single blood transfusion or surgery are able to provide more precise time intervals from infection to cirrhosis and HCC. Although the mean time to cirrhosis in chronic HCV patients is estimated at 20 years, only 10–20% of patients will actually develop cirrhosis within this time period [19]. A systematic review of 111 studies analyzing natural history estimated that the prevalence of cirrhosis 20 years after infection was 16% (95% CI 14–90%) [20]. Lower and higher estimates have been reported, depending in part upon the study design.

The 5- and 10-year survival rates of compensated cirrhosis are 90–95% and 70–80%, respectively. Hepatic decompensation of cirrhosis occurs at a rate of 3–4% per year. The cumulative probability of an episode of clinical decompensation is 5–10% at 1 year, and increases to 30–40% at 10 years, from the diagnosis of cirrhosis. Once decompensated cirrhosis occurs, the 5-year survival rate falls to 40–50%. Asian patients with HCV are more likely to be female, less likely to give a history of risk factors, present to medical services at an older age, and have more severe liver disease at diagnosis, but disease progression and response to treatment are similar to White patients [21].

Development of HCC

Virtually, all HCV-related HCC occurs among patients with cirrhosis. In a meta-analysis of 21 case–control studies, the risk for HCC was increased 17-fold in HCV-infected patients compared to HCV-negative controls [22]. The risk of HCC occurrence is different among all HCV patients. It is a function of the degree of liver fibrosis and the time of acquisition of the infection.

Once cirrhosis is established, HCC develops at an annual rate of 1–4% and is increased in patients with raised α-fetoprotein levels at baseline. Higher estimates in the range of 5–7% have been reported from Japan. The higher proportion of elderly patients infected with HCV in Japan may explain the higher incidence rate in this country, since older age accelerates the development of HCC. Patients with lesser degree of fibrosis have HCC development at rates of 0.5–2.6% [23]. In a recent systematic review of data relating to 2,386 patients, it was found that in compensated HCV cirrhosis, the estimated annual rate of death/transplantation was 4.58%, that of decompensation was 6.37%, and that of HCC was 3.36%. When compared with studies of untreated patients, studies that included treated patients reported significantly lower mean annual percentage rates of HCC (2.52 vs. 4.79%, $p = 0.02$), but not decompensation (5.34 vs. 7.88%, $p = 0.026$) and death/transplantation (3.79 vs. 4.62%, $p = 0.25$) [24]. The risk appears to be greater with genotype 1b compared with genotypes 2a/c [25].

In contrast to hepatitis B virus infection, HCC in patients with hepatitis C occurs almost exclusively in those with cirrhosis suggesting that cirrhosis is the major risk factor. There is also suggestive experimental evidence that HCV infection itself can promote the development of HCC.

Survival

Complications of hepatitis C are mostly confined to patients who have developed cirrhosis. This was illustrated in a prospective cohort study that included 838 patients with chronic HCV. During follow-up averaging 50 months, 62 patients died (31 from liver disease and 31 from other causes). An additional 30 patients developed nonlethal complications related to cirrhosis. Thus, approximately 7% of the cohort developed liver-related morbidity and mortality during follow-up. The increased mortality occurred only among patients who had cirrhosis at the time of presentation [26].

Survival is decreased in patients with HCV, especially in those who have developed cirrhosis. In a series of 384 patients with compensated cirrhosis, the 3-, 5-, and 10-year survival rates were 96, 91, and 79%, respectively [27]. Once decompensated cirrhosis occurs, the 5-year survival declines substantially to around 50%. Survival may also be worse in patients who develop cryoglobulinemia.

Causes of death among patients with HCV vary, based on the age group being examined. In a population study from Denmark, the primary cause of death among patients aged 20–39 years was unnatural (reported as death due to mental and behavioral disorders related to psychoactive substance use and death resulting from external causes). The 10-year risk of unnatural death in patients between the ages of 20 and 29 years was 13%. In patients between the ages of 40 and 59 years, deaths were equally distributed between liver-related, non-liver-related, and unnatural causes. In patients aged 70 years or older, the most common causes of death were non-liver related. Patients with HCV were at increased risk of death compared with non-HCV-infected individuals at all ages, ranging from an

18-fold increase for 20 to 29 years old to a 1.6-fold increase for patients aged 70 years or older [28].

Mortality in patients with HCV is not always related to liver disease. A population-based study from Australia found that most deaths in young patients with HCV were due to continued drug use rather than from the infection [29].

Once complications of cirrhosis have occurred, liver transplantation is the only effective therapy. Recurrent HCV infection of the graft occurs in almost all patients, although the long-term survival after transplantation for HCV is similar to that for other causes of hepatic failure (60–80%).

Factors predictive of disease progression

Several factors may be important determinants of disease progression in individual patients.

Age at acquisition and duration of infection

Age at the time of initial infection has been shown to correlate positively with rate of disease progression, even after controlling the duration of infection. Acquisition of HCV infection after the age of 35–55 years may be associated with a more rapid progression of liver injury [30]. Children appear to have a relatively decreased risk of disease progression. But, how the rate of fibrosis progression changes over an individual's lifetime, after controlling for other important predictors, is unclear.

Sex

Most reports of fibrosis progression in CHC have demonstrated faster progression to cirrhosis in males. Male sex has also emerged as an important risk factor for HCC in CHC [31].

Source of infection

Early reports of transfusion-associated hepatitis C demonstrated progression to cirrhosis in 15–27% of patients after a mean follow-up of 20 years. This rapid rate of progression far exceeded those observed in cohorts of community-acquired or childhood-acquired hepatitis C. However, another analysis that corrected for age found no significant difference among the various routes of infection [32].

Race and ethnicity

African-American patients with CHC have a higher rate of HCC and liver-related mortality when compared with White subjects. Paradoxically, African-Americans have lower ALT levels and hepatic activity and have a slower rate of fibrosis progression than non-African-American patients. It is possible that the observed increase in liver-related mortality is due to decreased access to care in African-American patients [33]. Relative to White patients, faster progression to cirrhosis has been suggested in Latino patients living in the United States. North American indigenous people have been found to have an enhanced rate of clearance during acute HCV infection as well as spontaneous clearance of chronic infection [34].

A recent study from United Kingdom evaluated the natural history of HCV infection and the outcome of therapy in an Asian population originating from the Indian subcontinent as compared to a group of White patients, using data collected as part of the Trent HCV study. Asian patients were more likely to be older, female, infected with genotype 3 and to consume no alcohol. At the time of first biopsy, fibrosis stage was significantly higher in Asian patients than in Whites (3.0 ± 2.3 vs. 1.8 ± 2.0, $p < 0.001$) as were necro-inflammation and steatosis scores. A longer duration of infection and the older age at presentation may explain the higher fibrosis scores on biopsy seen in Asian patients as, in those patients where duration of infection could be estimated, fibrosis progression was similar for both groups (0.25 ± 0.31 vs. 0.16 ± 0.54 Ishak points/year, $p = 0.068$) [21]. Far Eastern origin has also been suggested as a risk factor for progression in HCV cirrhosis, particularly with regard to HCC development, with cumulative probability of developing HCC in HCV patients to be 18% in 10 years in Japan [35]. It is not entirely clear whether this is due only to host characteristics or whether viral differences or the environment might also play a role.

Host genetic factors

Numerous studies have implicated polymorphisms of specific genes in rate of fibrosis because of CHC, but sample sizes have been small and results difficult to reproduce. Early studies focused on HLA major histocompatibility complex classes I and II alleles. Of the class II alleles, DRB1*1101, DDRB1*1104, DRB1*1302, and DQB1*0604 have been associated with low hepatitis activity and normal ALT levels. In contrast, DRB*0405 and DQB1*0401 have been associated with disease progression [16].

Polymorphisms of TGF-β1 and angiotensin II, poor metabolizer polymorphisms of CYP2D6 and microsomal epoxide hydrolase gene, polymorphisms of apolipoprotein E 4, mannose binding lectin, solute carrier family 11 member 1, matrix metalloproteinases, and the polymorphism responsible for hyperhomocysteinemia may be

significantly associated with disease progression in CHC. One recent report describes a set of 11 genetic polymorphisms, primarily involved in extracellular matrix turnover and immune response that distinguished between F1 and F2 fibrosis [36]. Case–control studies have failed to confirm an association between CCR5-δ32 and HCV disease severity. It is still unclear whether the genetic variation at the IL28B locus affects the severity and the pace of progression of liver disease due to CHC. While some investigators found that the unfavorable rs12979860 T/T gene pattern was associated with worse liver fibrosis [37], others did not replicate this finding [38, 39]. A recent study to assess the potential association between IL28B polymorphisms and the rate of progression of liver fibrosis, in a cohort of well-characterized patients for whom an accurate estimation of the date of infection could be obtained, found that IL28B genotype was not associated with fibrosis progression rate or with the risk of developing advanced liver fibrosis [40].

A genome-wide association study for functional single nucleotide polymorphisms was conducted in two separate cohorts of more than 400 CHC patients each to examine whether there were any associations with advanced fibrosis. A total of 1,609 "hits," or candidate genes, were identified in the initial cohort, but only <10% of these have thus far undergone validation [41]. Searching for host genetic polymorphisms that make a significant contribution to the variability in the course of CHC involves enormous complexity and difficulties.

Alcohol consumption

Multiple studies have shown that chronic alcohol intake with levels of consumption $\geq$ 50 g/day is associated with an increased rate of fibrosis progression in hepatitis C. Excessive alcohol intake has also been associated with an increased risk of both HCC and overall mortality. Alcohol promotes the progression of chronic HCV, even in patients with a relatively low alcohol intake. Alcohol increases HCV replication and has also been linked to the acceleration of liver injury [42]. Even moderate amounts of alcohol appear to increase the risk of fibrosis in patients with steatosis.

Smoking

Smoking is an independent predictor for progression of fibrosis in patients with CHC, even after controlling for alcohol consumption. Moreover, daily use of marijuana has been associated with development of steatosis and more rapid fibrosis progression, possibly through stimulation of endogenous, hepatic cannabinoid receptors [43].

Iron overload

Mild to moderate iron overload, because of hepatic inflammation and possibly viral-induced modification in iron trafficking, occurs in 30–40% of patients with CHC and has been associated with accelerated fibrosis. Accelerated fibrosis also occurs in patients with hepatitis C and hereditary or secondary hemochromatosis and heterozygous mutations of the hemoglobin β-chain. Association between heterozygous C282Y or H63D HFE mutations and advanced fibrosis in HCV remains inconclusive.

Coinfection with schistosomiasis

Concomitant CHC and schistosomiasis is common in many areas of the world. Relative to patients with CHC alone, several studies have reported increased hepatic inflammation and fibrosis in coinfected patients, particularly so in coinfection with *Schistosoma mansoni.*

Coinfection with hepatitis B virus

A complex interplay exists between these two viruses, typically manifested by reciprocal interference with replication leading to a variety of possible virologic profiles. The most frequent outcome is dominance by one virus with suppression of the other. Overt (hepatitis B surface antigen positive) chronic hepatitis B virus infection in the setting of CHC is associated with higher ALT levels, more rapid development of fibrosis and cirrhosis, and a substantially increased risk of HCC. Occult hepatitis B virus infection, on the other hand, does not appear to accelerate disease progression or impair treatment-induced clearance of HCV but does enhance the risk of HCC.

Coinfection with HIV

The progression of CHC is accelerated in HIV-infected patients. Among those with persistent HCV infection, HIV-1 coinfection has been associated with higher HCV plasma RNA viral loads and, in most studies, with more rapid progression to cirrhosis, liver failure, and HCC. In a meta-analysis of eight cohorts of HIV-1/HCV-coinfected individuals, Graham et al. [44] demonstrated that HIV-1 coinfection increased the risk of cirrhosis by a factor of 2.1 and clinically decompensated liver disease by a factor of 6.1.

Coffee consumption

Regular coffee consumption was associated with a low rate of disease progression among participants in the hepatitis C antiviral long-term treatment against cirrhosis (HALT-C)

trial—a long-term study of maintenance peginterferon in patients with advanced HCV infection [45]. In other studies, coffee consumption has been associated with reduced hepatic fibrosis and a low risk of HCC among patients with HCV infection [46].

Metabolic factors: steatosis, insulin resistance, and obesity

Hepatic steatosis and steatohepatitis may occur in CHC, particularly in the obese, but also independent of obesity. Steatosis, whether because of metabolic or viral factors, contributes to disease progression in CHC. Steatosis, on the initial biopsy, has been associated with faster development of fibrosis, higher risk of HCC, and decreased response to antiviral therapy. The association of steatosis with fibrosis, which is strongest in genotype 3 infections, is independent of age, sex, and alcohol consumption.

In CHC, diabetes mellitus and/or insulin resistance are independently associated with more severe fibrosis. Teasing out the relative contribution of obesity in the progression of CHC separate from the effects of steatosis, steatohepatitis, and insulin resistance is challenging. The observed association between high body mass index and fibrosis is confounded by underlying relationship with steatosis and diabetes.

Thus, the relationship between body mass, insulin resistance, steatosis and clinical outcomes is complex. In a study of 985 patients who had been enrolled in the HALT-C trial (a study of long-term peginterferon), the presence of insulin resistance was the strongest predictor of clinical disease progression overall, but the risk varied according to baseline histologic features. The presence of steatosis on a baseline biopsy was associated with worse clinical outcomes in those with bridging fibrosis, while low rates of adverse clinical outcomes were observed among those with steatosis and cirrhosis at baseline. The presence of Mallory bodies and significant weight gain ($\geq$5%) within a year of randomization were also associated with worse clinical outcomes [47].

Viral genotype

Data regarding the role of viral genotype in predicting outcome are too contradictory to reach definitive conclusions. Several studies showed a more aggressive disease progression for genotype 1b when compared to genotypes 2 and 3 [48, 49], with others showing genotype 3 to be associated with steatosis and disease progression [50–52]. There are other studies, however, that show a lack of correlation between viral genotype and disease progression [53, 54]. One recent study concluded that HCV genotype 1 is associated with a high rate of spontaneous clearance when compared to genotypes 2 and 3, but among patients who remain HCV RNA positive, genotype 1 behaves in a more aggressive manner [55]. While some reports have suggested that genotype 1b is overrepresented among patients with cirrhosis and those with HCC [56, 57], other studies found no such association after adjusting for disease duration or patient age [53, 58]. This suggests a cohort effect (i.e., patients infected with genotype 1b having had the disease for longer period).

The course of genotype 4 infection is similar to that of other genotypes [59, 60]. The fibrosis progression rate in genotype 4 is similar to that of patients infected with other genotypes; the presence of schistosomiasis is a negative predictor of outcome, being associated with accelerated progression of hepatic fibrosis among HCV-4 patients [61]. A recent study from Hong Kong found that both genotypes 1 and 6 have comparable liver biochemistry, HCV viral load, and similar rates of development of cirrhotic complications and mortality [62].

Another observation is that the disease may be accelerated in patients who are infected by more than one HCV genotype suggesting that coinfection may have an additive or synergistic harmful effect [59].

Other viral factors

The effect of viral factors on disease progression is less certain. The size of the infectious inoculum (viral dose) does not appear to be important. Data regarding the role of viral quasispecies in predicting outcome remain inconclusive.

Liver biopsy findings

The best clinical predictor of disease progression in chronic HCV infection is the amount of inflammation and fibrosis on liver biopsy. In a study of 70 patients with chronic HCV infection, patients with mild inflammation (portal inflammation alone or with only focal periportal extension) and no fibrosis had only a 1.2% annual risk of progressing to cirrhosis; patients with moderate chronic hepatitis (periportal inflammation usually involving more than 30% of the limiting plate) had a 4.6% annual risk of developing cirrhosis; more than 90% developed cirrhosis within 20 years of the time of the biopsy (which was not the onset of infection). Nearly, all patients with severe inflammation or bridging fibrosis developed cirrhosis within 10 years [63]. Stainable iron in hepatocytes has also been shown to predict progression and clinical and histologic outcomes in patients with advanced CHC [64].

CHC virus infection in patients with normal versus raised serum aminotransferases

The HCV infection with a normal ALT is defined by detectable HCV RNA and serum ALT concentration that is persistently within the normal range. Using this definition, approximately 25–40% of patients with chronic HCV infection have persistently normal serum ALT.

As a general rule, the cutoff values for normal in the laboratory reference range should be used. However, there are data to suggest that lower values for normal should be used. It has been proposed that the upper limit of normal may be set too high because of unrecognized fatty liver disease among apparently healthy individuals who were included in the cohorts used to establish the normal range. This is supported by a study in which a fall in ALT levels was noted in patients with "normal" ALT levels who achieved a sustained virologic response (SVR) after undergoing treatment [65].

The serum HCV RNA concentration does not correlate with the serum ALT. In one report, anti-HCV positive blood donors with normal ALT concentrations were older, and more often women, than those with abnormal levels [66]. In a study from Japan, HCV-infected patients with a normal serum ALT were much more likely to be HLA-DR13 positive than those with an elevated ALT (42 vs. 4%) [67].

The role of viral characteristics in determining the likelihood of a normal ALT state is unclear. In one review of 341 anti-HCV positive patients, those infected with genotype 3 were more likely to have a normal ALT, while those infected with genotype 2 were more likely to have an elevated ALT [68]. However, others have found a higher risk of having an elevated ALT in patients with genotype 1 [69] or, more commonly, no relation to viral genotype at all [70]. Other virologic characteristics, such as quasispecies diversity, have not been found to differ among patients with normal or increased serum ALT [71].

Many anti-HCV positive patients with normal serum ALT concentrations have an abnormal liver biopsy, although the changes are usually mild. Patients with a persistently normal ALT are more likely to be women, generally having milder disease, a low serum HCV RNA level, and a relatively favorable prognosis, although up to 10% of patients have bridging fibrosis suggesting that the relatively favorable prognosis is not universal [72].

A significant proportion of patients (20–30%) experience ALT flare that may be associated with enhanced disease progression [73]. Short-term studies suggest that the disease progresses slowly in the absence of regular alcohol intake. Most of these patients have been infected for 10–20 years before being identified as having HCV infection, suggesting that their overall prognosis is good. For example, in a study of over 200 patients with chronic HCV infection, one-half had a normal serum ALT. Over the 4-year course of the study, the patients with a normal ALT had one-half the rate of fibrosis progression compared with those with an elevated ALT; severe fibrosis was associated with alcohol consumption in these patients. The projected median time to cirrhosis for those with a normal ALT was 80 years [74]. A later report compared the characteristics of 480 patients with persistently normal ALT levels with 1,993 patients with elevated ALT levels. Significantly, more patients with a normal ALT level were women (59 vs. 32%), and the serum HCV RNA titer was significantly lower. Patients with a normal ALT level had significantly lower inflammation and fibrosis scores but almost two-thirds had portal fibrosis and 0% had bridging fibrosis. There was no correlation between serum ALT activity, HCV RNA level, and liver histology among patients with a normal ALT. ALT activity increased above the upper limit of normal in 53% of patients during 72 weeks of follow-up, while HCV RNA remained detectable in all patients [72].

Recurrence of HCC posthepatectomy in patients with HCV-related HCC is also dependent on posthepatectomy aminotransferase levels. The recurrence rate of HCC in hepatectomized patients with sustained low levels of ALT was found to be significantly lower (14.3 vs. 75%) than that in those patients whose ALT levels showed several peaks or plateaus [75].

Predictive models for disease progression

Many multivariate models that can help predict disease progression in individual patients have been developed. Baseline data collected as part of the HALT-C trial were used to develop predictive models for both clinical and histologic outcomes. The 1,050 patients in the HALT-C trial were previous nonresponders to standard interferon therapies who had advanced fibrosis on liver biopsy. Clinical outcomes were defined as an increase in Child–Pugh score to seven or greater, variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and liver-related death. The histologic outcome for the study was an increase in Ishak fibrosis score of two or more points (biopsies taken at 1.5 and/or 3.5 years after randomization). Factors predictive of clinical outcomes on multivariable analysis were elevated AST/ALT ratio, elevated total bilirubin, low albumin, low platelet count, and increasing Ishak fibrosis score. Factors predictive of histologic progression were increasing body mass index, low platelet count, and hepatic steatosis [74]. In another study, clinical and laboratory variables among 247 patients with varying degrees of HCV histologic severity were analyzed. Death from liver failure, development of HCC, and liver

transplantation were considered together in the statistical analysis. A history of hepatic decompensation (defined as at least one episode of ascites, jaundice, hepatic encephalopathy, or gastrointestinal bleeding of variceal origin) and the serum albumin concentration were independent predictors of the above outcomes. Patients without a history of decompensation and a serum albumin concentration >4.1 mg/dL (41 g/L) had only a 3% chance of developing one of the endpoints within 5 years compared to approximately 6% in patients with one of these factors, and 40% in patients with both factors [75]. In a third study of 455 patients who were followed for a median of 4.7 years, the only independent predictors of progression on multivariable analysis were sporadic transmission, advanced fibrosis, and a low albumin [76].

Effect of antiviral therapy and natural history of HCV infection

Emerging data demonstrate that interferon-based therapy, particularly among those achieving a SVR, is associated with long-term persistence of SVR, improved fibrosis and inflammation scores, reduced incidence of HCC, and prolonged life expectancy [77–79]. This reduction in the rate of progression has also been demonstrated in patients with CHC and cirrhosis, in some studies. The majority of these results are reported with standard interferon therapy, and long-term results of peginterferon plus ribavirin therapy with a higher likelihood of SVR should have a yet greater impact on the population of treated patients. The impact on slowing progression is greatest in patients with SVR, less in relapsers, and equivocal in nonresponders.

Antiviral therapy and effect on hepatic fibrosis and inflammation

A meta-analysis of data from 1,013 patients from three large randomized trials demonstrated that interferon treatment reduced inflammation and fibrosis in patients with SVR or who relapsed but not in nonresponders. This improvement was more prominent with use of peginterferon rather than interferon [80]. Even in patients with advanced fibrosis or cirrhosis, inflammation and fibrosis are improved with interferon monotherapy, peginterferon monotherapy, or peginterferon plus ribavirin combination therapy [81]. On the whole, studies of antiviral therapy with interferon monotherapy, peginterferon monotherapy, or peginterferon plus ribavirin combination therapy demonstrate an improvement in inflammation and fibrosis in patients with SVR, to a lesser extent in relapsers, and uncertain benefit in nonresponders.

Antiviral therapy and effect on incidence of HCC

Among chronic HCV infected without advanced fibrosis or cirrhosis, incidence of HCC is decreased in patients with SVR, and probably also in relapsers when compared with nonresponders [82, 83]. However, a reduction in the risk of HCC does not necessarily indicate improvement in overall survival, and interferon is less effective in patients with cirrhosis. In addition, cirrhotic patients tend to be older, and liver-unrelated mortality may be significant and obscure any potential benefit of interferon therapy. A few studies have shown that in patients with advanced fibrosis and/or cirrhosis who achieved SVR, the age-adjusted hazard ratio for developing HCC and death is significantly reduced [84]. A Japanese study has shown that gain in HCC-free survival following interferon treatment is greater in younger patients and more advanced fibrosis [79]. A failure to achieve SVR was associated with a high risk of liver-related complications, HCC, and liver-related mortality compared to those who achieved SVR [85]. However, several studies have demonstrated no beneficial effect of interferon therapy on the prognosis of cirrhotic patients. A recently published meta-analysis demonstrated that antiviral treatment was associated with a reduced risk of HCC in patients who attained SVR, compared with nonresponders; the best outcomes were seen in patients treated with ribavirin-based regimes [86]. The attainment of SVR also demonstrated prevention of the development of esophageal varices [87].There have been case reports and long-term follow-up studies that have shown the development of HCC in patients with advanced hepatic fibrosis after the achievement of SVR. These observations underscore the continued risk of HCC and need for ongoing surveillance with imaging and α-fetoprotein testing in patients with CHC and advanced hepatic fibrosis or cirrhosis, even after SVR.

Antiviral therapy and effect on life expectancy

It is expected that long-term durability of SVR, improvement in fibrosis and inflammation, and a reduced incidence of HCC would translate into a prolonged life expectancy. Interferon treatment decreases the risk ratio for overall death and liver-related death, particularly in patients with SVR, while the risk of liver-unrelated death remains unchanged [78, 84, 88, 89].

Conclusions

The heterogeneity in HCV clearance during acute HCV infection across individuals remains to be explained fully. Host genetic variation is assumed to explain the

heterogeneity to some extent; however, most variability in spontaneous HCV clearance remains unexplained. The relative importance of many and varied factors remains to be unfolded.

Despite the progress in understanding the factors affecting progression of CHC, a great deal remains to be learnt. Demographic and environmental variables account for 20–30% of the variation noted in rates of fibrosis progression rates [90]. The remainder of the variation may be accounted for by yet unknown variables (particularly host genetic factors), although statistical aberrations (i.e., concept of competing risks) may also exert an effect. Competing risks are events that prevent an event of interest from occurring. Competing risks might explain some of the relationship between disease progression and other factors that are independently associated with death, such as sex, race, coinfection with HBV or HIV-1, alcohol or tobacco use, and metabolic factors. This concept has been applied to fibrosis progression in CHC, where in a simulation experiment, competing risks from natural mortality accounted for half of the observed rate of fibrosis progression related to age at infection and may explain how the observed rate of fibrosis may appear to accelerate over time despite a constant underlying biologic rate [91], although this approach remains controversial [92]. The relative importance of many and varied factors remains uncertain, and further research efforts should be directed toward design of predictive models for effective risk stratification.

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