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Journal of Hepatology 44 (2006) S19–S24

Journal of Hepatology

www.elsevier.com/locate/jhep

Natural history and predictors of disease severity in chronic hepatitis C

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Cirrhosis is the end-stage consequence of fibrosis progression in patients with chronic hepatitis C. The median time from infection to cirrhosis is 30 years, with a high inter-individual variability, which is now better understood. Several factors have been clearly shown to be associated with fibrosis progression rate: duration of infection, age, male gender, alcohol consumption, HIV co-infection and low CD4 count. Metabolic conditions such as steatosis, being overweight and diabetes are emerging as independent co-factors of fibrogenesis. The recent validation of non-invasive biomarkers should facilitate the study of fibrosis progression in large populations.

***Keywords*: Hepatitis C; Cirrhosis; Fibrosis; Natural history**

1. Introduction

The major hepatological consequence of hepatitis C virus (HCV) infection is the progression to cirrhosis and its potential complications: haemorrhage, hepatic insufficiency and primary liver cancer [1].

Current understanding of HCV infection has been advanced by the concept of liver fibrosis progression [2,3]. Fibrosis is the deleterious but variable consequence of chronic inflammation. It is characterised by the deposition of extracellular matrix component leading to the distortion of the hepatic architecture with impairment of liver microcirculation and liver cell functions. HCV is usually only lethal when it leads to cirrhosis, the last stage of liver fibrosis. An estimate of fibrosis progression therefore represents an important surrogate endpoint for evaluation of the vulnerability of an individual patient and for assessment of the impact of treatment on natural history [2,3].

2. Fibrosis stages and necro-inflammatory activity grades

Activity and fibrosis are two major histological features of chronic hepatitis C that are included in different proposed classifications [4–7]. One of the few validated scoring systems is called the METAVIR scoring system [6,7]. This system assesses histological lesions in chronic hepatitis C using two separate scores, one for necro-inflammatory grade (A for activity from A0 to A3) and another for the stage of fibrosis (F from F0 to F4 cirrhosis).

Activity grade, which represents the necrosis feature, is not a good predictor of fibrosis progression [2,8], and fibrosis alone is the best marker of ongoing fibrogenesis [2,3,8,9]. Fibrosis stage and inflammatory grade are correlated but for approximately one-third of patients there is discordance. Clinicians should not take a 'significant activity' as a surrogate marker of 'a severe disease'. The clinical hallmarks of major necrosis and inflammation (i.e. severe acute hepatitis and fulminant hepatitis) are very rare in hepatitis C compared with hepatitis B. Even in immunologically compromised patients there are very few acute flare-ups in patients with chronic hepatitis C.

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doi:10.1016/j.jhep.2005.11.009

3. The dynamic view of fibrosis progression

Fibrosis stage summarises the vulnerability of a patient and is predictive of the progression to cirrhosis [2,3,9,10]. There is a strong correlation for fibrosis stages with age at biopsy and duration of infection. This correlation was not observed between activity grades [2,3,9].

The informative value of fibrosis stage allows the assessment of the speed of the fibrosis progression. The distribution of fibrosis progression rates suggests the presence of at least three populations: a population of 'rapid fibrosers', a population of 'intermediate fibrosers' and a population of 'slow fibrosers'. Therefore, the expression of a mean (or median) fibrosis progression rate per year (stage at the first biopsy/duration of infection) and of a mean expected time to cirrhosis does not signify that the progression to cirrhosis is universal and inevitable. Using the median fibrosis progression rate, in untreated patients, the median expected time to cirrhosis is 30 years; 33% of patients have an expected median time to cirrhosis of less than 20 years and 31% of patients will progress to cirrhosis after more than 50 years or will never progress to cirrhosis [2,3,9,10].

The limitations of any estimate of fibrosis include: (i) the difficulty in obtaining paired liver biopsies; (ii) the necessity for a large numbers of patients to achieve statistical power; and (iii) the sample variability in fibrosis distribution. Because the time elapsed between biopsies is relatively short (usually between 12 and 24 months), events (transition from one stage to another) are rare. Therefore the comparisons between fibrosis progression rates require a large sample size to observe significant differences. The rate of progression is difficult to assess because there is no large database with several biopsies. The real rate is therefore unknown and even if there is a linear relationship between stages and age at biopsy or duration of infection, other correlations are possible [11–13]. Using a large database we confirmed that the fibrosis progression was mainly dependent on the age and the duration of infection with four different periods—very slow, slow, intermediate and rapid progression rates [9,10].

Furthermore, liver biopsy has its own limitations for the assessment of liver fibrosis. Although it is the gold standard for scoring fibrosis, its value is limited by very high sample variability [13–16]. Future studies using validated non-invasive biochemical markers, such as FibroTest™, should improve modelling of fibrosis progression [17–20].

4. Factors associated with fibrosis progression

Factors associated and not associated with fibrosis are summarised in Table 1. Several factors have been shown to be associated with fibrosis progression rate: duration of infection, age, male gender, heavy consumption of alcohol, HIV co-infection, low CD4 count and necrosis grade [2,3,9,10,21–23]. The progression from infection to cirrhosis depends strongly on age, either expressed by duration of infection, by age at infection or age at last biopsy [9,10]. Metabolic conditions such as obesity, steatosis and diabetes are emerging as independent co-factors of fibrogenesis [24–27].

4.1. Age

The role of ageing in fibrosis progression could be related to higher vulnerability to environmental factors (especially oxidative stress), or to reduction in blood flow, mitochondria capacity or immune capacities [26]. The effect of age on fibrosis progression is so important (Fig. 1) that modelling the hepatitis C epidemic without taking age into account is not possible. The estimated probability of progression per year for men aged 61–70 years was 300-times greater than that for men aged 21–40 years [9,10]. Age of transplanted liver has also been associated with higher fibrosis progression rates [27].

4.2. Male gender

Males have a 10-times more rapid progression to cirrhosis than females, regardless of age [10]. Oestrogen modulates fibrogenesis in experimental injury, blocks proliferation and fibrogenesis by stellate cells in primary

Table 1
Factors associated or not with fibrosis progression

Associated in uni- and multi-variate analysis	Not sure	Not associated
Fibrosis stage	Inflammation	Last serum viral load
Age at infection	Haemochromatosis heterozygote	Genotype non-3
Duration of infection	Cigarette consumption	Mode of infection
Age at biopsy	Moderate alcohol consumption	Liver viral load
Consumption of alcohol >50 g per day	Genotype 3	
HIV co-infection	Schistosomiasis	
CD4 count <200/ml		
Male gender		
Necrosis		
Body mass index and or diabetes and/or steatosis		

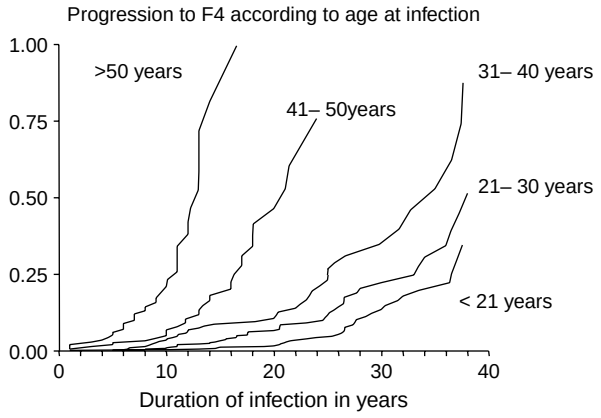

Fig. 1. Probability of fibrosis progression to cirrhosis (F4) in patients with hepatitis C virus infection, according to age at infection. Modeling in 2313 patients with known duration of infection [31].

culture, and may modify the expression of transforming growth factor and other soluble mediators [23]. We observed that when metabolic factors were taken into account the association between male gender and fibrosis was reduced [28] but also that long term estrogen exposure reduces liver fibrosis progression in women [29].

4.3. Alcohol

The role of alcohol consumption has been established for daily intake greater than 40 or 50 g per day [2,9,21,22]. For lower intake, there are discordant results with even preliminary studies suggesting a protective effect of very small quantities of alcohol. Alcohol consumption is difficult to quantify and conclusions must be prudent. However it seems that the influence of alcohol is independent from other factors, weaker than the influence of age, and is exerted only at toxic levels of intake.

4.4. HIV co-infection

Several studies have demonstrated that patients co-infected with HCV and HIV (and not treated) have more rapid fibrosis progression than mono-infected patients or other patients liver diseases, even after taking into account age, sex and alcohol consumption [9,30–32]. A HIV-infected patient with less than 200 CD4 cells/μl and drinking more than 50 g of alcohol daily has a median expected time to cirrhosis of 16 years versus 36 years for a HIV-infected patient with more than 200 CD4 cells/μl and drinking 50 g or less of alcohol daily [22].

4.5. HCV viral genotype

Viral factors such as genotype, viral load at the time of the biopsy, and quasi species are not associated with fibrosis [2,9,32–34]. An association with fibrosis and genotype 3 is suspected, because of the steatosis associated with this genotype [9,35–37].

4.6. Risk of fibrosis in patients with normal transaminase levels

Patients with repeatedly normal serum transaminase activity have a lower fibrosis progression rate than matched control patients with elevated transaminases [9,38,39]. However, 15–19% of patients with normal transaminase levels have moderate or high fibrosis progression rates. We therefore recommend assessment of the fibrosis stage with liver biopsy or biochemical markers in these PCR positive patients. If the patient has avanced fibrosis with a high fibrosis rate, treatment should be considered. Fibrotest™ has the same predictive value in patients with normal or elevated transaminases [18]. In patients aged 65 years or older, extensive fibrosis and normal transaminases are frequently observed and this population is particularly at risk of high fibrosis progression rates [40].

5. Metabolic factors

5.1. Impact of steatosis on the pathogenesis of chronic hepatitis C

With a few exceptions [41,42], steatosis is associated with more severe necro-inflammatory activity [43,44] or fibrosis [36,44–49], even after adjustment for age [42]. Steatosis is also associated with a higher cumulative incidence of hepatocellular carcinoma, independent of age, cirrhosis and treatment with interferon [49]. The fibrosis progression rate appeared to be higher when marked steatosis [42]. Few studies with follow-up biopsies are available. A faster progression of fibrosis in patients with steatosis on the first biopsy has been observed, but the small sample size precludes an analysis according to the genotype [46]. Other studies suggested that the increase in steatosis rather than the total amount of steatosis may be indicative of fibrosis progression [45].

No study has documented an association between steatosis and fibrosis independent of other confounding factors. In one study, an apparent association between steatosis and fibrosis disappeared after adjustment for serum glucose and BMI, thus casting doubt on the true relevance of steatosis per se to fibrogenesis [28].

5.2. Impact of diabetes on the pathogenesis of chronic hepatitis C

Although many studies have documented an epidemiological association between hepatitis C and type 2 diabetes, only a few have focused on its consequences for liver injury [50]. Fibrosis stage is usually higher in diabetics, but results are discordant when taking into account other well-identified

risk factors of liver fibrosis [48,50–53]. In the largest study to date, performed on 710 patients with a known duration of infection, a high serum glucose (as well as overt, drug-treated diabetes) was associated with more advanced liver fibrosis as well as a higher fibrosis progression rate, independent of other risk factors of fibrosis [28]. The fibrogenic impact of high serum glucose was higher than the impact of obesity, suggesting that measurement of blood glucose could provide more accurate information on the fibrogenic potential of underlying insulin resistance than the measurement of the body mass index [28].

A common caveat of these transversal observational studies is that cirrhosis-induced alterations of glucose homeostasis may confound the relationship between a high serum glucose and/or diabetes and liver fibrosis. Some studies still documented a significant association after exclusion of cirrhotic patients [28]. High serum glucose is associated with intermediate and advanced stages of fibrosis but not with early stages, suggesting a more important role in the perpetuation and progression of fibrogenesis rather than in initiation [28].

5.3. Impact of obesity on the pathogenesis of chronic hepatitis C

Overall, obesity seems to worsen liver histology in chronic hepatitis C. One study has documented a highly significant association between obesity and steatosis and between steatosis and fibrosis, but no direct association was found between obesity and fibrosis [54]. Obese patients have more advanced fibrosis stages than lean patients, but this does not appear to be independent of other confounding factors such as a high serum glucose and/or diabetes [28,52,53]. These discrepancies may result from the fact that none of these studies makes the distinction between visceral and peripheral obesity: only visceral obesity is correlated to insulin resistance and its complications, in particular hepatic steatosis [55,56].

As a consequence of the complex interactions between insulin resistance and liver injury, it is difficult to analyse the specific contribution of obesity.

Several authors have attempted to identify, on histological grounds alone, the presence of lesions compatible with non-alcoholic steatohepatitis (NASH) in obese patients with chronic hepatitis C. Their assumption is that these two fibrogenic conditions would increase liver fibrosis when occurring together, which in turn would demonstrate the contribution of obesity to fibrosis in HCV-infected patients. Unfortunately, the two conditions share many common histological lesions, which makes it difficult to assert the presence of NASH in chronic hepatitis C. The attributable risk of NASH to liver fibrosis in obese patients with hepatitis C may not be determined until more specific markers of NASH are identified.

Preliminary data demonstrates that after a 3-month period of controlled weight loss through diet and exercise, nine out of 10 patients with hepatitis C had reduced steatosis and five out of 10 had less fibrosis [57]. Weight loss was associated with improved insulin sensitivity. Although sampling variability of liver biopsy is a significant concern in such a small sample size, the demonstration that cellular markers of stellate cell activation were also turned off in patients with reduced weight and less fibrosis, further strengthens the hypothesis of a deleterious impact of obesity in chronic hepatitis C. Furthermore, surgical treatment of obesity decreases fibrosis [58].

5.4. Interaction between genotype and metabolic factors

Fibrosis was associated with steatosis only in genotype 3 infected individuals and with past alcohol abuse and diabetes only in non-3 genotype infected patients [59]. Other studies showed that hepatitis C virus may induce insulin resistance and accelerate fibrosis progression—this effect seemed to be genotype 3 specific in one study [60] but not in a study in mild hepatitis C [61].

6. Conclusion

Tremendous progress has been achieved in the comprehension of fibrosis progression in patients with chronic hepatitis C. The role of ageing and metabolic factors is particularly important for therapeutic decisions. The treatment of hepatitis C with interferon and ribavirin combination is very effective for blocking fibrosis progression and can even induce reversal of cirrhosis, a concept unthinkable 10 years ago. Unfortunately, even in developed countries, death due to hepatitis C is increasing because of inadequate detection and treatment.

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