Journal of Hepatology 51 (2009) 626–627

Journal of Hepatology

www.elsevier.com/locate/jhep

Editorial

Forewarned is forearmed ☆

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The hepatitis C virus comprises 6 genotypes and more than 100 subtypes. While differences in the virologic response rates to peginterferon alfa plus ribavirin combination therapy are well established, less evidence has been accumulated regarding whether HCV genotypes are associated with differences in the natural course of disease. No clinically relevant differences with respect to symptoms and extrahepatitic manifestations of chronic hepatitis C according to HCV genotypes are reported. The published data on the impact of HCV genotypes on fibrosis progression rates, development of cirrhosis, and the risk for hepatocellular carcinoma are somewhat conflicting leading to the overall perception that clinically relevant differences are non-existant. Studies on the possible association of HCV genotype with the fibrosis progression rates are complicated by confounding factors, e.g. by the fact that HCV-1b infected patients in several regions are older than HCV-1a and HCV-3a infected patients and typically show substantial differences with respect to transmission risk factors [1–3].

The study by Bochud et al. [4] is one of the largest data sets on the association of HCV genotypes and fibrosis progression rates. The data of this study indicate a faster fibrosis progression rate in patients infected with HCV genotype 3 compared with patients infected with HCV genotype 1, supporting some previous smaller studies which showed a similar trend [5,6].

The methodology of the study by Bochud et al. is sound since the authors used both a stage-constant and a stage-specific estimation of fibrosis progression rates according to different HCV genotypes, together with cumulative incidence curves. The concordant observation that HCV genotype 3 was associated with accelerated fibrosis both in stage-specific and stage-constant fibrosis rate estimates in a large cohort of well-characterized patients make the data appear robust. A possible limitation of the study as outlined in the discussion of the paper [4] is the fact that the estimated duration of infection was based on the first event at risk, which may not be accurate. Furthermore, biopsy specimens were not read by a central pathologist and the authors cannot rule out other confounding factors, e.g. that patients infected with HCV genotype 3 infection may have had a higher exposure to liver-toxic agents beyond alcohol (e.g. continuous use of illicit drugs). Thus, some concerns remain as in most studies with a cross-sectional design, and the data should be confirmed in other cohorts and if at all possible in prospectively designed trials.

What are the practical consequences if indeed fibrosis progression rates are faster in patients infected with HCV genotype 3 ? First, comprehensive counselling of patients with respect to proven (alcohol consumption) or suspected concomitant factors (overweight, iron overload) is mandatory. Second, reluctance to defer or delay antiviral therapy may not be appropriate. Generally, sustained virologic response rates in patients chronically infected with HCV genotype 3 are high. Combination therapy with peginterferon alfa and ribavirin for 24 weeks achieves sustained virologic response rates of 70–80% [7,8]. In patients with low baseline viral load (<800,000 IU/mL) and a rapid virologic response

Associate Editor: M. Colombo

☆ The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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doi:10.1016/j.jhep.2009.06.010

treatment duration can be shortened to 16 weeks without compromising SVR rates [9]. However, in patients with high baseline viral load (>800,000 IU/mL) and/or without a rapid virologic response virologic relapse rates after 24 weeks of combination therapy are high [9,10]. Retrospective analyses suggest that this subpopulation may benefit from 48 weeks of combination therapy including higher doses of ribavirin (1000–1200 mg/day) [8,11]. Prospective trials are ongoing to finally answer this open question. No study has yet specifically studied treatment success in HCV genotype 3-infected patients with liver cirrhosis, but clinical experience shows that SVR is difficult to achieve in this population.

Due to marked improvement in SVR rates for HCV-1 infected patients treated with peginterferon alfa, ribavirin, and a NS3 serine protease inhibitor [12–14], treatment is currently delayed in many patients to await approval of these specifically targeted antiviral therapies (STAT-C drugs). All physicians treating patients with chronic hepatitis C, however, should be reminded that the clinically most advanced protease inhibitors telaprevir and boceprevir are mainly active against HCV genotypes 1 (and 2) and less active against HCV genotypes 3 and 4 [15,16]. Similarly, non-nucleoside polymerase inhibitors are generally active against HCV-1 isolates [17]. Activity against HCV-3 isolates has yet been documented only for nucleoside polymerase inhibitors (e.g. R7128) and cyclophilin inhibitors (e.g. Debio-025) [18,19]. Taken together, combination of peginterferon alfa and ribavirin could remain the key treatment option for patients infected with HCV genotype 3 in the years to come. If indeed fibrosis progression in patients infected with HCV genotype 3 is faster than in HCV-1 infected patients, waiting for new treatment options should be strongly discouraged in this patient population.

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