Antiviral Treatment of HCV-related Chronic Hepatitis: Is the Cup half Empty, or half Full?

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Hepatitis C Virus (HCV) is one the main causes of chronic liver disease (CLD), cirrhosis, hepatocellular carcinoma (HCC) and liver-related mortality, and constitutes the most common indication for liver transplantation (1,2). Although the therapy of HCV-related chronic hepatitis (CH) has greatly improved in the last years and definitive HCV eradication is now a reality in many patients, antiviral treatment is far from being safe and effective, and many issues remain to be solved. For example, how should we treat previous relapsers and non responders (3); which HCV carriers with persistently normal ALT levels should be treated (4); should *difficult* patients (e.g., genotype 1, overweight, high viral load, more severe degree of fibrosis, etc.) receive more "aggressive" treatment (5); and finally, might the results from international clinical trials (6-8) be reproduced in the everyday clinical practice?

In the March 2007 issue of this Journal, Gheorghe *et al* (9) did provide convincing evidence that individualized weight-based treatment with pegylated interferon (PEG-IFN) α2b plus ribavirin represented a suitable approach for patients with HCV-related CH and negative predictive factors for sustained virological response (SVR).

The current standard of care for HCV CH is now represented by combination therapy with PEG-IFNs plus ribavirin (3). Two PEG-IFNs are available: PEG-IFN α2a, administered at a fixed dose (180 μg/kg weekly), and PEG-IFN α2b, administered at a weight-based dose (1.5 μg/kg weekly). The results of large clinical trials (6-8) support the recommendation that patients with HCV-1 require 48 weeks of combination therapy with high ribavirin doses (1000-1200 mg daily, depending on weight < or > 75 kg, respectively), while "easy-to-treat" patients (HCV-2 and 3 genotypes) can be treated for only 24 weeks with a lower ribavirin dose (800 mg daily). It has been recently suggested that HCV genotype 2 might be treated for shorter periods (10). Available studies (3,5,6-9) have clearly shown that antiviral combined treatment can allow SVR in 50-55% of the patients (from 40 to 50 % of people harbouring genotype 1 and up to 80 % of those with non-1 HCV genotype).

Therapy is clearly indicated for patients with CHC, circulating HCV RNA, moderate to severe fibrosis (METAVIR ≥ F2) and no contraindications to treatment (3-5). ALT elevation is no more a prerequisite for therapy (11), although people with persistently normal ALT levels and/or mild histological liver damage usually show lower risk of progression towards more severe forms of liver damage (12,13). In cases where a decision is made to defer therapy in patients with mild disease and/or normal ALT, periodic biochemical follow-up and histological monitoring should be performed (3,5,14).

It is now universally accepted that the rate of sustained virological response (SVR) is based on several host, virus and environmental predictors: for example, it is well known that HCV-1 genotype, high viral load, bridging fibrosis or cirrhosis, overweight, steatosis, African-American ethnicity are associated with poor response rates to combination therapy (3,5). In particular, genotype 1 is the most important predictor of a low response to a standard of care treatment (3).

The management of patients with these negative predictors is a true challenge for doctors in clinical practice. The need for optimisation of therapy and for more personalized antiviral regimen according to individual patient features is often hampered by the high incidence of major side effects, which could crucially decrease the adherence to treatment.

The study of Gheorghe *et al* (9) was aimed at evaluating the rate of early virological response (EVR) and SVR in a group of patients with CHC genotype 1 treated for 48 weeks with PEG IFN α2b plus ribavirin. The results of this study are very interesting, as a SVR was seen in 56% of the patients, despite the *difficult-to-treat* genotype and the slight overweightness found in this series of patients. Definitive discontinuation of treatment due to major side

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effects was necessary in only 8.7% of the patients. This study is very intriguing, as it shows that the excellent results seen in large randomized clinical trials (RCTs) might be achieved also in real-life healthcare settings. Indeed, patients enrolled in large RCTs are usually "easier" (younger, higher willingness to be treated, higher compliance, lower prevalence of comorbidities) than the unselected population seen in everyday clinical practice (14).

How do we monitor the response to antiviral therapy? Several methods to quantify serum HCV RNA are available. It is now widely accepted that early evaluation of virological response to antiviral therapy has great relevance for the prediction of treatment outcome, as EVR strongly correlates with the long term virological response (15). Thus, the assessment of early response is now used to identify different sets of response (*flat* responders, rapid virological responders, "super" responders), and to early recognize those patients where treatment should be discontinued, given the low chance of sustained virological response (5). These findings allow the identification of a "stopping rule" policy in patients without early virological response, in order to avoid unnecessary prolongation of treatment. According to this strategy, in patients with genotype1, quantitative HCV RNA should be evaluated after 12 weeks of therapy. Patients showing HCV RNA negativity should continue treatment for 48 weeks, as they have a relatively high chance to obtain a SVR. On the other hand, therapy should be stopped in patients in which HCV RNA is persistently detected at week 12^{th}, unless quantitative levels show a drop of at least 2 $\log_{10}$ unit compared to baseline HCV RNA values. In the latter, HCV RNA should be further retested at week 24, and treatment should be continued only in the case of HCV RNA negativity (3,15).

In conclusion, the study of Gheorghe *et al* (9) adds further evidence that some negative predictors (such as HCV genotype and overweight) can be overcome by more individualized drug schedules, and that the promising results of international RCTs might be reproduced also in clinical practice. This is very important, as successful treatment has been shown to improve liver histology, to decrease fibrosis progression and to reduce the risk of cirrhosis and HCC, and thus mortality. As there is still a long way to go for novel approaches to CHC (HCV enzyme inhibitors, vaccines), only more aggressive and tailored antiviral protocols can also allow optimal results in everyday practice (16).

References

1. EASL International Consensus Conference on Hepatitis C. Paris, 26-28, February 1999, Consensus Statement. J Hepatol 1999; 30:956-961.
2. National Institutes of Health Consensus Development Conference Panel statement: management of hepatitis C. Hepatology 1997; 26: 2S-10S.
3. Dienstag JL, McHutchison JG. American Gastroenterological Association medical position statement on the management of hepatitis C. Gastroenterology 2006; 130: 225-230.
4. Puoti C. HCV carriers with persistently normal ALT levels: not too much healthy, not true patients. Rom J Gastroenterol 2004; 13 :329-332.
5. Strader DB, Wright T, Thomas DL, Seeff LB. American Association for the Study of Liver Diseases. Diagnosis, management and treatment of Hepatitis C. Hepatology 2004; 39: 1147-1171.
6. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon a-2b plus ribavirin compared with interferon a-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358:958–965.
7. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347:975–982.
8. Hadziyannis SJ, Sette H Jr, Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004;140: 346–355.
9. Gheorghe L, Iacob S, Sporea I, et al. Efficacy, Tolerability and predictive factors for early and sustained virologic response in patients tTreated with weight-based dosing regimen of pegIFN alpha-2b and ribavirin in real-life healthcare setting. J Gastrointestin Liver Dis 2007; 16: 23-29.
10. Mangia A, Santoro R, Minerva N, et al. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. N Engl J Med 2005;352:2609–2617.
11. Puoti C, Castellacci R, Montagnese F et al. Histological and virological features and follow-up of hepatitis C virus carriers with normal aminotransferase levels: the Italian prospective study of the asymptomatic C carriers (ISACC). J Hepatol 2002; 37: 117-123.
12. Puoti C. HCV carriers with persistently normal aminotransferase levels: normal does not always mean healthy. J Hepatol 2003; 38:529-532.
13. Alberti A. Towards more individualised management of hepatitis C virus patients with initially or persistently normal alanineaminotransferase levels. J Hepatol 2005; 42: 266-274.
14. Puoti C, Bellis L, Martellino F et al. Surveillance of patients with chronic hepatitis C not on antiviral therapy: a practical approach. Rom J Gastroenterol 2005; 14: 141-146.
15. Alberti A, Benvegnu L. Management of hepatitis C. J Hepatol 2003; 38: S104-S118.
16. McHutchison JG, Bartenschlager R, Patel K, Pawlotsky JM.The face of future hepatitis C antiviral drug development: recent biological and virologic advances and their translation to drug development and clinical practice. J Hepatol 2006; 44: 411-421.