

Editorial

DOI: 10.1111/j.1478-3231.2010.02437.x

Treatment of chronic hepatitis B with telbivudine: wise hepatologists needed in hepatitis B endemic countries where treatment options are limited

After a hectic decade of fast progress in hepatitis B drug development, the hepatitis community is left with seven licensed drugs for treating patients with chronic hepatitis B (CHB). These are two interferon molecules, the classic interferon α and its pegylated form, and the nucleos (t)ide analogs (NAs) lamivudine, adefovir, entecavir, telbivudine and tenofovir (1, 2). Pegylated interferon has replaced the classic one in clinical practice because of its better pharmacokinetics and pharmacodynamics and its once weekly easier use. Among the NAs, entecavir and tenofovir are the preferred oral antivirals mainly as a result of their potent antiviral efficacy combined with a high genetic barrier to resistance (3), which led to the recommendation of both the EASL and the AASLD hepatitis B guidelines to consider them as first-line oral treatment options (1, 2). The decision on how to treat a patient with CHB relies mainly on whether treatment with pegylated interferon with a finite treatment duration is chosen or treatment with entecavir or tenofovir for prolonged if not indefinite treatment duration. The most widely used surrogate marker of treatment success, undetectable hepatitis B virus (HBV) DNA in serum, is less often achieved with the former approach but because durable HBeAg seroconversion in HBeAg-positive CHB (4, 5) and the best treatment end point, HBsAg clearance, may be seen more often with pegylated interferon (6), it is still used to some extent despite the plethora of side effects observed and several host and viral factors limiting its use (1, 2, 7, 8). Overall, however, NAs are used much more often for the treatment of CHB (9, 10).

In this issue of *Liver International*, two manuscripts dealing with CHB treatment have appeared. Both manuscripts report mainly on telbivudine as a treatment option in CHB. In the study by Gane *et al.* (11), efficacy and safety of 3 years of telbivudine treatment are reported and in the study by Safadi *et al.* (12) treatment response of switching to telbivudine of patients treated previously with lamivudine is assessed. At a time where in treatment-naïve patients, both entecavir and tenofovir appear to be superior drugs when compared with telbivudine, how relevant is the study by Gane and colleagues for the overall liver community? In patients who are on lamivudine treatment, is a study assessing a treatment strategy consisting of switching to a more potent drug that, however, is cross-resistant to the drug used clinically relevant? The answers to such questions are not a

universal 'no' as one might expect but depend largely on where one lives. In the industrialized western world, mainly Europe and North America, both studies may appear as not relevant as both entecavir and tenofovir appear to be superior to telbivudine as noted above; hence, use of telbivudine under the conditions reported in both papers may not appear of clinical importance.

However, there may be other aspects to consider. A recent analysis by Liaw (13) gives clues why both studies could be potentially important. This review reports that in most parts of Asia, hepatitis B treatment is reimbursed only with limitations or not at all. Prolonged treatment with oral antivirals means high cost and when the patient himself or herself has to pay even partially, optimal treatment may not be affordable. Further, at least for the time-being, not all drugs are available everywhere including the Far East. These considerations have important consequences because half of patients dying from hepatocellular cancer, the third most common cause of cancer-related death, are from China and most of the rest from Africa (14). In such areas, both studies may have enormous clinical implications which, given the contribution of these regions to overall hepatocellular carcinoma incidence, are not just of regional but of global significance. Telbivudine may not be cheaper than tenofovir or entecavir in the west (15), but in other regions of the world this may be different.

Analysis of the GLOBE study comparing telbivudine vs. lamivudine for the treatment of CHB suggested that there may be a relatively large subgroup of patients where close to current oral antiviral-induced optimal treatment outcome can be obtained with telbivudine using the so-called roadmap concept (16, 17). Basically, patients who have high alanine aminotransferase (ALT) levels combined with low HBV DNA at commencement of treatment, i.e. 9 or 7 \log_{10} copies/ml of HBV DNA for HBeAg-positive and HBeAg-negative CHB, respectively, may be the most suitable patients for treatment with telbivudine. In such patients, a low rate of resistance at 2 years (around 2%) has been reported for both HBeAg-positive and HBeAg-negative CHB when patients had concomitant serum HBV DNA of < 300 copies/ml at 6 months of treatment (16). The study by Gane *et al.* (11) report the outcome in these patients after 3 years of telbivudine treatment and attracts attention. Overall, they report a cumulative HBeAg seroconversion rate of 46% and a genotypic resistance rate of 10% in HBeAg-positive CHB.

When the roadmap concept was applied to the same group of patients, cumulative HBeAg seroconversion of 58% was achieved after 3 years of treatment with a genotypic resistance rate of 2.7%. It is noteworthy that such a seroconversion rate compares fairly well with both entecavir and tenofovir (18, 19). One may speculate that with very potent antivirals, immune hepatitis B virus epitopes needed for mounting an immune response may also diminish; these, however, may be required for HBeAg seroconversion.

Similarly, in HBeAg-negative CHB, overall HBV DNA undetectability is reported as 85% and genotypic resistance as 5.4%. Further, 87% of patients who had undetectable HBV DNA at 6 months of treatment remained HBV DNA negative after 3 years of treatment. Genotypic resistance was detected in 5% of patients in this group. These data are interesting. However, the data should be interpreted with caution and in its right context. The GLOBE study provided important information because all patients who entered the study were followed for 2 years and results were assessed by an intention-to-treat analysis. This is no longer the case in the 3-year assessment. After 2 years of treatment, patients were free to stop treatment, to receive a different treatment or continue in this open-labelled extension study. However, patients who had developed resistance to telbivudine during 2 years of treatment were not allowed to enter the open-label study. Further, of 92 patients who did not continue in the extension study at their own or the investigator's discretion, only 32 patients had undetectable HBV DNA at the end of the GLOBE study. It is thus important to concentrate not on the overall response rates but to assess those who would apply to the roadmap concept. The former approach obviously overestimates response rates. The application of the roadmap concept is prone to less bias when one considers that patients who have undetectable HBV DNA at month 6 of treatment were also less likely to have had detectable HBV DNA at 2 years of treatment. However, that 13% of patients with undetectable HBV DNA at 6 months of treatment did not continue to maintain this at 3 years of treatment indicates a need to closely follow these 'good responders' and suggests that, even here, the response rates may be overestimated.

The roadmap concept suggests switching to or adding an antiviral not cross-resistant to the primary compound in patients on telbivudine or lamivudine not reaching HBV DNA undetectability at 6 months of treatment. In a patient who is on lamivudine, with the current armamentarium of oral antiviral drugs, the best fit would be to add/switch to tenofovir. What to do if the patient was started on lamivudine and tenofovir is not available. Without doubt, adding adefovir to lamivudine would be the way to go (20, 21). Safadi *et al.* (12) have assessed the strategy of switching from lamivudine to telbivudine. Briefly, in this study, patients who had received 3–12 months of lamivudine were assigned 1:1 to either to switch to telbivudine or continue on lamivudine for

another 52 weeks. All patients had to have a serum HBV DNA level of at least 1000 copies/ml at study entry. The study was a randomized, double-blind, multicentre global study conducted in 246 HBeAg-positive and HBeAg-negative CHB patients. The primary endpoint was the reduction in serum HBV DNA levels from baseline at week 24. Patients who switched to telbivudine had a better mean HBV DNA reduction than patients who continued on lamivudine. However, viral breakthrough occurred with similar frequency in both treatment groups; only in patients who had lamivudine exposure for < 24 weeks was telbivudine treatment associated with less viral breakthrough and the authors therefore suggested an early switch to telbivudine. Patients who failed on telbivudine had had lamivudine-resistance mutations during the preceding lamivudine treatment.

Where do we go from here? The answer is again region related. For the industrialized world, it simply confirms that a drug with cross-resistance to the primary compound used is not the right choice. For most of the rest of the world, it suggests that if a physician were to use telbivudine in a patient on lamivudine, this should be carried out as early as possible (before 6 months).

The two studies may in part reflect the dilemma of physicians and patients alike in regions of the world where treatment options are restricted. In these regions, the best strategy for hepatitis B management should begin with optimal characterization of the patient in need of treatment. If possible, treatment should be started at a time point at which they are most likely to respond, i.e. when patients have elevated transaminases and low serum HBV DNA. This best response baseline assessment applies to both interferons and NAs. Such patients are more common than one may think as low HBV DNA and high ALT are a combination that is unavoidable in the HBV natural history and readily seen in clinical practice (22). Active hepatitis B disease means an active immune response of the host and is the main reason for progression of disease if left untreated. This active immune response would lead to elevated ALT and decreasing levels of HBV DNA. Such a strategy cannot be applied to patients with compensated or decompensated cirrhosis where treatment commencement cannot be postponed. However, in CHB cases of mild or moderate severity, this strategy of 'wait and intervene with treatment at the optimal moment' appears to be the best option in areas where treatment options are limited. Thus, 'wise hepatologists' are needed in these parts of the world. The two papers in the current issue of *Liver International* can be seen as a clinical scientific contribution of how suboptimal treatment options can be applied with the best possible outcomes.

Cihan Yurdaydin¹ and Ulus S. Akarca²

¹ Department of Gastroenterology, University of Ankara and Hepatology Institute, University of Ankara, Ankara, Turkey

² Department of Gastroenterology, Ege University, Izmir, Turkey

References

1. EASL clinical practice guidelines: management of chronic hepatitis B. *J Hepatol* 2009; **50**: 227–42.
2. Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. Available at <http://www.hepatology.org>
3. Woo G, Tomlinson G, Nishikawa Y, *et al.* Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. *Gastroenterology* 2010; **139**: 1218–29.
4. Van Nunen AB, Hansen BE, Suh DJ, *et al.* Durability of HBeAg seroconversion following antiviral therapy for chronic hepatitis B: relation to type of therapy and pre-treatment serum hepatitis B virus DNA and alanine aminotransferase. *Gut* 2003; **52**: 420–4.
5. Reijnders JG, Perquin MJ, Zhang N, *et al.* Nucleos(t)ide analogues only induce temporary hepatitis e antigen seroconversion in most patients with chronic hepatitis B. *Gastroenterology* 2010; **139**: 491–8.
6. Marcellin P, Piratvisuth T, Brunetto MR, *et al.* A finite course of peginterferon alfa-2a results in inactive chronic hepatitis B and HBsAg clearance 5 years post-treatment in patients with HBeAg-negative disease: baseline characteristics and predictive factors of long-term response (abstr). *Hepatology* 2009; **50**: 487A.
7. Buster EHCJ, Hansen BE, Lau GKK, *et al.* Factors that predict response of patients with hepatitis B e antigen – positive chronic hepatitis B to peginterferon-alfa. *Gastroenterology* 2009; **137**: 2002–9.
8. Bonino F, Marcellin P, Lau GKK, *et al.* Predicting response to peginterferon alfa-2a, lamivudine and the two combined for HBeAg-negative chronic hepatitis B. *Gut* 2007; **56**: 699–705.
9. Lampertico P, Colombo M. HBeAg-negative chronic hepatitis B: why do I treat my patients with nucleos(t)ide analogs. *Liver Int* 2009; **29**(Suppl. 1): 130–2.
10. Coffin CS, Lee SS. Treatment of HBeAg-positive patients with nucleos(t)ide analogues. *Liver Int* 2009; **29**(Suppl. 1): 116–24.
11. Gane E, Wang Y, Liaw YF, *et al.* Efficacy and safety of prolonged 3-year telbivudine treatment in patients with chronic hepatitis B. *Liver Int* 2011; **31**: 676–84.
12. Safadi R, Xie Q, Chen Y, *et al.* Efficacy of switching to telbivudine in chronic hepatitis B patients previously treated with lamivudine. *Liver Int* 2011; **31**: 667–75.
13. Liaw YF. Antiviral therapy of chronic hepatitis B: opportunities and challenges in Asia. *J Hepatol* 2009; **51**: 403–10.
14. Ferenci P, Fried M, Labrecque D, *et al.* World Gastroenterology Organisation Guideline. Hepatocellular carcinoma (HCC): a global perspective. *J Gastrointest Liver Dis* 2010; **19**: 311–7.
15. Hoofnagle JH. Therapy of hepatitis B. Unresolved issues and remaining challenges. AASLD 2010, Postgraduate Course Book, pp. 52–5.
16. Zeuzem S, Gane E, Liaw YF, *et al.* Baseline characteristics and early on-treatment response predict the outcomes of 2 years of telbivudine treatment of chronic hepatitis B. *J Hepatol* 2009; **51**: 11–20.
17. Keefe EB, Zeuzem S, Koff RS, *et al.* Report of an international workshop: roadmap for management of patients receiving oral therapy for chronic hepatitis B. *Clin Gastroenterol Hepatol* 2007; **5**: 890–97.
18. Heathcote EJ, Gane E, deMan RA, *et al.* Long term (4 year) efficacy and safety of tenofovir disoproxil fumarate treatment in HBeAg-positive patients with chronic hepatitis B (study 103): preliminary analysis (abstract). *Hepatology* 2010; **52**: 556A.
19. Pan C, Tong MJ, Kowdley KV, *et al.* Long-term entecavir treatment for up to 5 years in Asian patients with HBeAg-positive nucleos(t)ide naïve chronic hepatitis B: results from ETV-022 and -901 (abstract). *Hepatology* 2010; **52**: 557A.
20. Lampertico P, Vigano M, Manenti E, *et al.* Low resistance to adefovir combined with lamivudine: a 3-year study of 145 lamivudine-resistant hepatitis B patients. *Gastroenterology* 2007; **133**: 835–42.
21. Idilman R, Kaymakoglu S, Önder FO, *et al.* A short-course of add-on adefovir dipivoxil treatment in lamivudine-resistant chronic hepatitis B. *J Viral Hepat* 2009; **16**: 279–85.
22. Hadziyannis SJ, Vassilopoulos D. Hepatitis B e antigen-negative chronic hepatitis B. *Hepatology* 2001; **34**: 617–24.