Telbivudine: Taking into account baseline and on-therapy predictors

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Telbivudine versus lamivudine in patients with chronic hepatitis B. Lai CL, Gane E, Liaw YF, Hsu CW, Thongsawat S, Wang Y, Chen Y, Heathcote EJ, Rasenack J, Bzowej N, Naoumov NV, Di Bisceglie AM, Zeuzem S, Moon YM, Goodman Z, Chao G, Constance BF, Brown NA; Globe Study Group.

***Background*: Reducing hepatitis B virus (HBV) replication to minimal levels is emerging as a key therapeutic goal for chronic hepatitis B.**

***Methods*: In this double-blind, phase-3 trial, 1370 patients with chronic hepatitis B were randomly assigned to receive 600 mg of telbivudine or 100 mg of lamivudine once daily. The primary efficacy end point was non-inferiority of telbivudine to lamivudine for therapeutic response (i.e., a reduction in serum HBV DNA levels to fewer than 5 log10 copies per milliliter, along with loss of hepatitis B e antigen [HBeAg or normalisation of alanine aminotransferase levels). Secondary efficacy measures included histologic response, changes in serum HBV DNA levels, and HBeAg responses.**

***Results*: At week 52, a significantly higher proportion of HBeAg-positive patients receiving telbivudine than of those receiving lamivudine had a therapeutic response (75.3% vs. 67.0%, $P = 0.005$) or a histologic response (64.7% vs. 56.3%, $P = 0.01$); telbivudine also was not inferior to lamivudine for these end points in HBeAg-negative patients. In HBeAg-positive and HBeAg-negative patients, telbivudine was superior to lamivudine with respect to the mean reduction in the number of copies of HBV DNA from baseline, the proportion of patients with a reduction in HBV DNA to levels undetectable by polymerase-chain reaction assay, and development of resistance to the drug. Elevated creatine kinase levels were more common in patients who received telbivudine, whereas elevated alanine aminotransferase and aspartate aminotransferase levels were more common in those who received lamivudine.**

***Conclusions*: Among patients with HBeAg-positive chronic hepatitis B, the rates of therapeutic and histologic response at 1 year were significantly higher in patients treated with telbivudine than in patients treated with lamivudine. In both the HBeAg-negative and the HBeAg-positive groups, telbivudine demonstrated greater HBV DNA suppression with less resistance than did lamivudine.**

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Antiviral drugs have changed the management and outcome of chronic hepatitis B, since they can cause a rapid decrease in HBV viremia followed by ALT normalisation and improvement in hepatic inflammation. The main problem in treating hepatitis B with antivirals is maintaining viral control over time, since they can cause viral resistance. In this context new potent antiviral drugs with a high genetic barrier may help clinicians in managing these patients.

Lai et al. [1], enrolled in a phase-3 trial, 1367 patients with chronic hepatitis B (either HBeAg positive or negative) randomly allocated to receive telbivudine 600 mg or lamivudine 100 mg once daily for 104 weeks. The sample size was calculated according to a non-inferiority design. The primary efficacy end point was a therapeutic response that included the reduction of serum HBV DNA to less than $5 \log_{10}$ copies/mL along with ALT normalisation and/or HBeAg loss; the histological response, the decline in HBV DNA and the percentages of patients achieving an undetectable HBV DNA by PCR were also assessed. This clear linear design with end points relevant to clinical practice and measured with updated methods on intention-to-treat basis adds value to the study. It is therefore simple for the reader to interpret the numbers and trace the patient outcome. However, lamivudine is no longer recommended as monotherapy for chronic hepatitis B [2–4]. Telbivudine has not been compared directly with entecavir or tenofovir, both of which proved to have a good resistance profile. Recent guidelines agree on recommending starting antiviral therapy in naïve patients using drugs with a high genetic barrier to ensure as prolonged viral suppression as possible. Does telbivudine meet these criteria?

At week 52, a significantly higher proportion of HBeAg-positive patients receiving telbivudine achieved a therapeutic response than those receiving lamivudine. Telbivudine was non-inferior to lamivudine in HBeAg-negative patients. In both groups telbivudine was superior to lamivudine with respect to the mean reduction in HBV DNA from baseline and in the pro-

☆ The author declared that he does not have a relationship with the manufacturers of the drugs involved, either in the past or in the present and did not receive funding from the manufacturer to carry out this research.

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portion of patients with undetectable HBV DNA at week 52.

Strictly speaking, telbivudine has a low genetic barrier since a single site substitution (M204I) induces resistance. Its strength resides in its rapid and profound antiviral action which contributes to improving the resistance profile. Nevertheless, in 5% of HBeAg positive and in 2.2% of HBeAg-negative patients genotypic resistance was detected after 52 weeks of therapy. Overall, looking from the perspective of the glass half full, 40% of HBeAg-positive and 12% of HBeAg-negative patients did not achieve HBV DNA undetectability. Residual viremia candidates these patients to develop resistance during the subsequent weeks of therapy. Indeed, the results at 104 weeks of continuous treatment, to date released in abstract form [5], show that genotypic resistance appears in 25% and 11%, respectively, of HBeAg-positive and HBeAg-negative patients.

These results could be optimised by using baseline and on-therapy predictors. Lai et al. [1] found that the achievement of an HBV DNA level $<3\log_{10}$ copies/mL at week 24 of therapy is predictive of more favourable 1-year outcomes. In this short-term period the main advantages were seen in HBeAg-positive patients, who achieved 90% undetectable HBV DNA and 41% HBeAg seroconversion at 1 year if they had presented an undetectable HBV DNA by week 24. Hence, telbivudine appears to be a valid option for a time-defined therapeutic course aimed at HBe seroconversion, provided the HBV DNA level is evaluated after 24 weeks of therapy.

The concept of "on-treatment" prediction has found wide consensus for antivirals (but not for interferons) and has been recommended for clinical practice in recent guidelines in order to maximise long-term response. For this purpose, an early switch or add-on strategy is the best choice for patients not achieving HBV DNA suppression by week 24, mainly if they are receiving antiviral drugs with low genetic barrier [4,6]. Again, head-to-head comparisons between recently approved antivirals are lacking.

A further analysis of the telbivudine trial [5] identified a low basal HBV DNA level ($<9\log_{10}$ copies/mL for HBeAg-positive patients and $<7\log_{10}$ copies/mL for HBeAg negative) as a positive predictor of response at week 104. Coupling a low basal viremia and the achievement of a negative HBV DNA at week 24 identified a subgroup with the best outcome at week 104, i.e., an undetectable HBV DNA in around 90% of cases and the emergence of genotypic resistance in about 2%. However, only a minority of the patients enrolled in the trial met these predictive criteria.

Is this sufficient for clinicians? Recent developments in anti-HBV drugs have led to a reformulation of the objectives of therapy towards complete viral suppression for years (10? life-long?) and possibly a clearance of HBsAg. In this context, two further issues are crucial, i.e., safety and costs. We are about to administer new antiviral drugs for years or for life to our patients on the basis of 1–2 year trials that are powered to measure differences in the efficacy outcomes, and on a few cases treated for longer periods. Safety of therapy is more difficult to extrapolate than efficacy. In the case of telbivudine, creatine kinase elevation and few cases of myopathy that emerged in the registrative trial [1,7] warrant caution and further consideration. New drug combinations, that are in theory highly effective, may also result in extra toxicities.

Lastly, the cost of antiviral therapy is becoming a crucial factor for clinical choices, due to the increasing number of patients under therapy and to local reimbursement policies. Once we have established the relative efficacy, resistance profile and safety of the different monotherapies or drug combinations over a sufficient duration, the choice must privilege the cheapest. Large observational cohort studies will cover these issues more exhaustively.

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doi:10.1016/j.jhep.2008.08.008