Chronic hepatitis B therapy with lamivudine in clinical practice

Summary of the discussion

Expert : J. Dixon, Glaxo Wellcome Research and Development, UK
Moderators : J. Delwaide, Ulg ; Y. Horsmans, UCL
Reporter : H. Van Vlierberghe, University of Ghent.

Question : When there is seroconversion (HBeAg negative, anti-HBe positive) after treatment with lamivudine, in which percentage of the patients is this seroconversion sustained ?

J. Dixon : When there is a seroconversion at the end of treatment with lamividine, the recurrence rate is comparable with that seen after interferon treatment. The response is sustained in about 85% of the patients.

Question : Is there a difference in occurrence of the YMDD variant during lamivudine between patients with chronic hepatitis, cirrhosis, or patients after liver transplantation ?

J. Dixon : The percentage of YMDD variants during lamivudine treatment is similar between the different patient groups. The figure varies between 16 and 27% after one year treatment. Recent data (Perillo *et al.*, 1999) suggest that in patients after liver transplantation the clinical implications can be more significant. In 32 transplant patients who were treated with lamivudine when hepatitis B (re)appeared, 14 developed a YMDD variant. Six of these 14 patients had a clinical deterioration of their graft function. However, data on patients who are treated in the pretransplant period to suppress the viral load and in whom the treatment is maintained after transplantation are lacking.

Question : When a YMDD variant occurs, is it helpful to associate other nucleoside analogues ?

J. Dixon : After the occurrence of a YMDD variant, accompanied by a rise in ALT level, three possibilities exist :

1. It is safe to take the patient off lamivudine. After stopping the treatment, the wild type virus will reappear and the physician can choose alternatives to treat the patient (interferon, thymosine,...)
2. At this moment, there is no evidence that the combination of lamivudine and other nucleoside analogues is helpful. However, GlaxoWellcome is coordinating a trial where after the development of a YMDD variant and the elevation of ALT, the lamivudine treatment is combined with low dose adefovir. The low dose may prevent adefovir-associated renal toxicity which is dose-duration-dependent. There is *in vitro* evidence that a low dose of adefovir is effective against YMDD variant HBV.
3. Data are lacking about the value of immunomodulatory drugs (interferon, thymosin) and lamivudine in the presence of YMDD variants.

Question : When, during treatment with lamivudine, there is a rise in ALT level, is this predictive of seroconversion ?

J . Dixon : Not necessarily, a rise in ALT level can also be the hallmark of the occurrence of a YMDD variant. However, the rise in ALT level as a consequence of a YMDD variant is mostly slow and less high than the rise seen during a flare up.

Question : Seroconversion is described even after the occurrence of a YMDD variant. Is the rate of seroconversion different from the rate seen in the absence of a YMDD variant ?

J. Dixon : The rate of seroconversion in patients with the YMDD variant seems to be lower than in patients without. Patients with elevated ALT treated for 4 years showed seroconversion in 41% of who had developed a YMDD variant and in 100% among those who did not develop YMDD variant (unpublished data).

Question : Is the incidence of YMDD variants in patients with a precore mutant similar as in patients with the wild type virus ?

J. Dixon : The frequency of YMDD variants in patients treated with lamivudine is similar in wild type virus and precore mutant infection.

Question : Does it make sense to treat patients with normal ALT levels with lamivudine ?

J. Dixon : Asian studies suggest that there may be some histological improvement, however, the seroconversion rate is low and comparable to placebo treatment.

Question : Does it make sense to treat HBsAg 'healthy carriers' with lamivudine ?

J. Dixon : No.

Question : Does it make sense to treat patients with acute hepatitis B ?

J. Dixon : Data are lacking. However, in more than 90% of the cases, an acute hepatitis B is self-resolving an no treatment is needed. Large trials would be necessary to define if lamivudine treatment is effective.

Question : What is the optimal duration of treatment with lamivudine ?

J. Dixon : Glaxo Wellcome suggests to continue treatment until seroconversion. In trials the rate of seroconversion after 1 year is about 20%.
F. Nevens : These are indeed the data seen in ideal conditions as trials are. In clinical practice the rate of seroconversion will be lower. This means for most patients a 'long' treatment.

Question : When after transplantation there is *de novo* infection with hepatitis B with high HBV DNA levels but with normal ALT, is treatment necessary ?

F. Nevens : In the KULeuven we saw 4 patients with the described characteristics. On liver biopsy they all had minimal changes but a high level of HBs and HBc immunostaining. Until now we did not treat these patients. It is, however, very important to vaccinate the partner. Recently, we saw a lung transplant patient with the same clinical picture, who, after being stable for several months, developed a fulminant liver failure and died.

Concluding remarks by the moderators (F. Nevens, Y. Horsmans)

- Lamivudine is the treatment of choice in the following conditions :
  a. Patients with decompensated hepatitis B cirrhosis waiting for liver transplantation
  b. Patients with hepatitis B (decompensated cirrhosis) after kidney transplantation (the response to interferon is low and carries the risk of rejection of the renal allograft)
  c. Prevention of recurrence after liver transplantation
- Lamivudine treatment can be an option in patients with precore mutants, as the response to interferon is low.
- In patients with chronic hepatitis B with the wild type virus no clear answer can be given whether lamivudine or interferon is the first choice.

Reference

PERRILLO R.P., SCHIFF E.R., DIENSTAG J.I. *et al.* Lamivudine for prevention of recurrent hepatitis after liver transplantation : final results of a US/Canadian multicenter trial. *Hepatology*, 1999, **30** : 222A.