J R Coll Physicians Edinb 2006; **36:**222

Combination therapy for chronic hepatitis B

K Simpson
Consultant Physician, Centre for Liver & Digestive Disorders, Royal Infirmary of Edinburgh, Edinburgh, Scotland

TITLE Entecavir for treatment of lamivudine-refractory, HBeAg-positive chronic hepatitis B

AUTHORS Sherman M, Yurdaydin C, Sollano J *et al.*

JOURNAL *Gastroenterology* 2006; **130(7):**2039–49.

KEYWORDS Chronic hepatitis B, antiviral therapy, drug resistance, lamivudine, entecavir.

LIST OF ABBREVIATIONS Alanine aminotransferase (ALT), hepatitis B virus deoxyribonucleic acid (HBV-DNA)

DECLARATION OF INTERESTS K Simpson is a member of the Bristol Myers Squibb and Novartis medical advisory boards.

Published online ***September 2006***

Correspondence to ***K Simpson, Centre for Liver & Digestive Disorders, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh, EH16 4SA***

tel. ***+44 (0)131 242 1621***

fax. ***+44 (0)131 242 1633***

e-mail ***k.simpson@ed.ac.uk***

SUMMARY

Chronic hepatitis B affects over 400 million people worldwide. Lamivudine, the first effective antiviral for chronic hepatitis, is limited by the frequent emergence of viral resistance. Continued treatment in spite of resistance has been advocated, but is associated with active disease, progressive liver damage, decompensated cirrhosis and hepatocallular carcinoma.

This paper reports the largest randomised controlled trial so far of antiviral (entecavir) therapy in lamivudine-resistant patients. Two-hundred and ninety three patients were randomised, 133 given entecavir reached 48 week endpoints, and 129 continuing on lamivudine reached 48 week endpoints. Entecavir proved statistically superior to continued lamivudine therapy in reaching two co-primary endpoints ($p < 0{\cdot}0001$); acheivement of a composite of HBV-DNA and ALT levels, and liver histological improvement. Entecavir was also superior in reaching other secondary endpoints. Adverse drug events were comparable, and three deaths were not related to drug therapy.

Entecavir in lamivudine-resistant patients was superior to continued lamivudine therapy. About 6% of patients had mutations associated with entecavir resistance at the start of the trial, indicating lamivudine selects for entecavir resistance, and two patients (<2%) developed entecavir resistance. Adefovir was suggested for those becoming entecavir resistance.

OPINION

This international trial adds further evidence for the efficacy of entecavir in chronic hepatitis B. Earlier studies have reported superior efficacy compared with lamivudine in HBeAg negative and HBeAg positive patients assessed by normalisation of serum transaminases and undetectable HBV-DNA by PCR.[2,3] However, many patients with chronic HBV are already on lamivudine and will have developed resistance to that drug. This paper shows that entecavir is efficacious in such patients. What was observed in this study, in comparison with the previous papers treating lamivudine-naive patients,[2,3] was the emergence of phenotypic and genotypic resistance in a small number of patients. Similar data has been reported with adefovir when treating lamivudine-resistant strains of HBV.[1]

Currently there are three effective antiviral drugs for chronic hepatitis B, yet many patients are treated sequentially with one drug added to another when viral resistance emerges. Initial monotherapy was justified when lamivudine was the only antiviral drug available. The challenge for the future is to embrace the lessons of the past. We don't treat tuberculosis with a single antibiotic, and hepatitis C and HIV are treated most effectively with antiviral combinations. The time has come to recognise that the most effective treatment for chronic hepatitis B lies in using combinations of antivirals; but what combination makes the finest blend? Time and appropriate trials will give us the answer.

REFERENCES

1 Angus P, Vaughan R, Xiong S *et al.* Resistance to adefovir dipivoxil therapy associated with the selection of a novel mutation in the HBV polymerase. *Gastroenterology* 2003; **125(2):**292–7.
2 Chang TT, Gish RG, de Man R *et al.*; BEHoLD AI463022 Study Group. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2006; **354(10):**1001–10.
3 Lai CL, Shouval D, Lok AS *et al.*; BEHoLD AI463027 Study Group. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2006; **354(10):**1011–20. Erratum in: *N Engl J Med* 2006; **354(17):**1863.