

Entecavir was more effective than lamivudine in HBeAg-positive chronic hepatitis B

Chang TT, Gish RG, de Man R, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med*. 2006;354:1001-10.

Clinical impact ratings: Gastroenterology ★★★★★☆ Infectious Disease ★★★★★☆

QUESTION

In patients with HBeAg-positive chronic hepatitis B without previous nucleoside analogue treatment (e.g., lamivudine or adefovir), what is the relative efficacy and safety of entecavir compared with lamivudine?

METHODS

Design: Randomized controlled trial (Benefits of Entecavir for Hepatitis B Liver Disease [BEHoLD]).

Allocation: Unclear allocation concealment.*

Blinding: Blinded (clinicians, patients, and outcome assessors).*

Follow-up period: 52 weeks.

Setting: 137 centers worldwide.

Patients: 715 patients ≥ 16 years of age with HBeAg-positive chronic hepatitis B and compensated liver function, detectable hepatitis B surface antigen for ≥ 24 weeks, evidence of HBV DNA ≥ 4 weeks before screening and HBV DNA ≥ 3 meq/mL at screening, and serum alanine aminotransferase (ALT) level 1.3 to 10.0 times the upper limit of normal. Exclusion criteria included hepatitis C or D or HIV coinfection; other forms of liver disease; use of interferon- α , thymosin- α , or antiviral agents in the past 24 weeks; previous lamivudine therapy > 12 weeks; α -fetoprotein level > 100 ng/mL; and history of ascites requiring diuretics or paracentesis.

Intervention: Entecavir, 0.5 mg once daily ($n = 357$), or lamivudine, 100 mg once daily ($n = 358$), for 52 weeks.

Outcomes: Histologic improvement (improvement by ≥ 2 points in the Knodell necroinflammatory score with no worsening in the Knodell fibrosis score at 48 wk). Secondary outcomes were reduction in HBV DNA level, proportion of patients with undetectable HBV DNA, decrease in the Ishak fibrosis score, HBeAg loss, HBeAg seroconversion, and normalization of serum ALT. The primary safety outcome was discontinuation because of adverse events.

Patient follow-up: 709 patients (99%) (mean age 35 y) received ≥ 1 dose of the study drug; 88% had adequate baseline liver biopsy specimens for assessment of the primary outcome.

MAIN RESULTS

Patients who received entecavir had greater histologic improvement than did patients who received lamivudine (Table). The entecavir group had a greater proportion of patients with undetectable HBV DNA and

ALT normalization (Table) and a greater reduction in HBV DNA level (6.9 vs 5.4 log copies/mL, $P < 0.001$). Entecavir and lamivudine groups did not differ for decrease in Ishak fibrosis scores, HBeAg loss, or HBeAg seroconversion (Table). The rate of adverse events was similar in the 2 groups. Fewer entecavir-group patients discontinued the study because of adverse events (1 vs 9 patients, $P = 0.02$).

CONCLUSION

In patients with HBeAg-positive chronic hepatitis B without previous nucleoside analogue treatment, entecavir led to greater histologic improvement than lamivudine and was well tolerated.

Source of funding: Bristol-Myers Squibb.

For correspondence: Dr. T.T. Chang, National Cheng Kung University Medical College, Tainan, Taiwan. E-mail tchang@mail.ncku.edu.tw. ■

*See Glossary.

Entecavir vs lamivudine for HBeAg-positive chronic hepatitis B at 48 weeks†

Outcomes	Entecavir	Lamivudine	RBI (95% CI)	NNT (CI)
Histologic improvement‡	72%	62%	16% (3.8 to 30)	11 (6 to 40)
Undetectable HBV DNA§	67%	36%	83% (57 to 115)	4 (3 to 5)
ALT normalization	68%	60%	14% (2.1 to 27)	12 (7 to 77)
HbeAg seroconversion	21%	18%	16% (-14 to 57)	Not significant

†ALT = alanine aminotransferase. Other abbreviations defined in Glossary; RBI, NNT, and CI calculated from data in article.

‡Improvement of ≥ 2 points in the Knodell necroinflammatory score with no worsening in the Knodell fibrosis score at week 48.

§HBV DNA < 300 copies/mL by polymerase chain reaction assay.

||ALT < 1.25 times the upper limit of normal.

COMMENTARY

Although hepatitis B infection has steadily declined since the introduction of systematic vaccination (1), chronic hepatitis B remains a significant problem. For example, in the United States, about 1 250 000 people have chronic hepatitis B, and of the 79 000 new cases/y (1), about 4000 will become chronic. 2 therapeutic approaches are available for this potentially lethal condition: interferons or virostatics, such as lamivudine or entecavir (2).

The well-powered study by Chang and colleagues compared entecavir with lamivudine. Some statistically significant but not very impressive differences favored entecavir. Viral breakthrough occurred in 2% and 18% in the entecavir and lamivudine groups, respectively. There was no viral resistance to entecavir by molecular analysis of the virus. The main problem with lamivudine is the emergence of resistant strains, which can reach up to 70% after 4 years of treatment (2).

Entecavir has recently been approved by the U.S. Food and Drug Administration for treatment of chronic hepatitis B. The choice between lamivudine, adefovir, or entecavir should be based on virology and cost: Adefovir and entecavir induce less resistance but cost U.S.

\$18 to \$20 per day, whereas lamivudine frequently induces resistance but costs only \$6 per day.

My approach to the patient with HBeAg-positive chronic hepatitis B is usually to prescribe an interferon first: Only for interferons do we have evidence of prolonging survival (2) and inducing loss of HBeAg in a sizable number of patients. However, the patient—given the cost and side effects of interferon—may favor a virostatic. In this case, a pragmatic approach would be to start with lamivudine and add a more potent but also more expensive second drug, such as adefovir or entecavir, when genotypic (increase in DNA > 1000 IU/mL) or phenotypic (increase in DNA and ALT) resistance evolves.

Jürg Reichen, MD
University of Berne
Berne, Switzerland

References

- Hepatitis B vaccination—United States, 1982-2002. *MMWR Morb Mortal Wkly Rep*. 2002;51:549-52, 563.
- Lok AS, McMahon BJ. Chronic hepatitis B: update of recommendations. *Hepatology*. 2004;39:857-61.