Peginterferon α-2a alone or combined with lamivudine increased response rates more than lamivudine alone

Marcellin P, Lau GK, Bonino F, et al. **Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B.** N Engl J Med. 2004;351:1206-17.

QUESTION

In patients with hepatitis B e antigen (HBeAg)–negative chronic hepatitis B, how do peginterferon α-2a monotherapy, peginterferon α-2a plus lamivudine, and lamivudine monotherapy compare for efficacy and safety?

METHODS

Design: Randomized controlled trial (Peginterferon Alfa-2a HBeAg-Negative Chronic Hepatitis B Study).

Allocation: Concealed.*

Blinding: Blinded {clinicians, data collectors, and outcome assessors}†.*

Follow-up period: 72 weeks.

Setting: 54 sites in 13 countries.

Patients: 552 patients (mean age 40 y, 85% men) who had been negative for HBeAg and positive for anti–hepatitis B e antibody and hepatitis B surface antigen for ≥ 6 months, had a hepatitis B virus (HBV) DNA level > 100 000 copies/mL, a serum alanine aminotransferase (ALT) level > 1 but ≤ 10 times the upper limit of the normal range, and had findings on liver biopsy in the previous 24 months consistent with chronic hepatitis B.

Intervention: Peginterferon α-2a, 180 μg once weekly, plus oral placebo once daily (n = 182); peginterferon α-2a, 180 μg once weekly, plus lamivudine, 100 mg once daily (n = 186); or lamivudine, 100 mg once daily (n = 184) for 48 weeks.

Outcomes: Normalization of ALT levels, suppression of HBV DNA levels to < 20 000 copies/mL, and adverse events.

Patient follow-up: 97% (intention-to-treat analysis).

MAIN RESULTS

Patients who received peginterferon α-2a monotherapy or peginterferon α-2a plus lamivudine had greater normalization of ALT levels and greater suppression of HBV DNA levels to < 20 000 copies/mL, but also had an increased rate of having ≥ 1 adverse event, than did patients who received lamivudine monotherapy (Table).

CONCLUSION

In patients with hepatitis B e antigen–negative chronic hepatitis B, peginterferon α-2a monotherapy and peginterferon α-2a plus lamivudine increased rates of normalization of alanine aminotransferase levels and suppression of hepatitis B virus DNA levels to < 20 000 copies/mL, but also increased adverse events compared with lamivudine monotherapy.

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*See Glossary.

†Information provided by author.

Peginterferon α-2a (P), peginterferon α-2a plus lamivudine (P + L), and lamivudine (L) for hepatitis B e antigen–negative chronic hepatitis B at 72 weeks‡

Outcomes	Comparisons	Event rates	RBI (95% CI)	NNT (CI)
Normalization of alanine aminotransferase levels	P vs L	59% vs 44%	34% (10 to 65)	7 (4 to 21)
	P + L vs L	60% vs 44%	35% (11 to 66)	7 (4 to 20)
Suppression of hepatitis B virus DNA levels to < 20 000 copies/mL	P vs L	43% vs 29%	47% (11 to 95)	8 (5 to 27)
	P + L vs L	44% vs 29%	51% (14 to 100)	7 (5 to 21)
			RRI (CI)	NNH (CI)
≥ 1 adverse event	P vs L	88% vs 48%	84% (58 to 119)	3 (3 to 4)
	P + L vs L	87% vs 48%	82% (56 to 116)	3 (3 to 4)

‡Abbreviations defined in Glossary; RBI, RRI, NNT, NNH, and CI calculated from data in article.

COMMENTARY

Chronic HBV infection affects about 350 million people worldwide, including 1.25 million in the United States (1). HBV increases risk for cirrhosis, hepatic decompensation, and hepatocellular carcinoma (2). About 5000 people die each year from complications of HBV (2).

The study by Marcellin and colleagues highlights the importance of using HBV DNA levels to define persistent infection, rather than conventional serologic markers. With such information, 3 patterns of chronic HBV infection are revealed (3). Most chronic HBV infection is found in Asia from perinatal transmission. Here, HBeAg persists longer, ALT levels tend to be normal, and serum HBV DNA levels may be high. Complications develop in the sixth or seventh decade of life, often after seroconversion. As many as 91% of patients have detectable HBV DNA levels after seroconversion of HBeAg (4).

In western countries, HBV is acquired during adulthood through sexual intercourse or parenteral drug use and has extremely low chronicity (< 5%), higher ALT levels, and good response to antiviral therapy. In Africa, Alaska, and Mediterranean countries, HBV is transmitted from person to person during childhood. Children who are positive for HBeAg have elevated ALT levels and seroconvert in late childhood or in their teens.

The availability of safe and easy-to-use drugs for HBV infection is important. Interferon α-2b, lamivudine, and adefovir dipivoxil have all been approved by the U.S. Food and Drug Administration for treatment of chronic HBV infection.

Single-drug therapy for patients with HBeAg–negative hepatitis appears to have poor response and can lead to drug resistance. Both interferon and lamivudine, used in this study, are associated with side effects and development of resistance if used for the long term. For these reasons, adefovir appears to be a better choice for single-drug, long-term treatment.

Various combination therapy trials are ongoing, and their results should be watched for further advances in therapy.

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