Note: This is a two-article spread with a shared commentary. Please scroll down for the second article.

THERAPEUTICS

The benefits of adefovir dipivoxil for HBeAg-negative chronic hepatitis B did not persist after discontinuation of treatment

Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. **Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B.** N Engl J Med. 2005;352:2673-81.

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

QUESTION

In patients with hepatitis B e antigen (HBeAg)–negative chronic hepatitis B who have received treatment with adefovir dipivoxil for 48 weeks, is continuing the drug for another 48 weeks more effective than stopping it?

METHODS

Design: Randomized placebo-controlled trial (Adefovir Dipivoxil 438 Study).

Allocation: Unclear allocation concealment.*

Blinding: Blinded (clinicians and patients).*

Follow-up period: 48 weeks.

Setting: {32 sites in Canada, Greece, Israel, France, Italy, Australia, Taiwan, and Singapore.}†

Patients: 120 patients (median age 47 y, 82% men) with HBeAg-negative chronic hepatitis B and compensated liver disease, who had received treatment with adefovir dipivoxil during the previous 48 weeks as part of a randomized placebo-controlled trial. Inclusion criteria were {age 16 to 65 years}†, detectable hepatitis B surface antigen (HBsAg) for ≥ 6 months, undetectable HBeAg, detectable anti-HBeAg, serum hepatitis B virus (HBV) DNA level ≥ 10^5 copies/mL, and serum alanine aminotransferase (ALT) level 1.5 to 15 times the upper limit of normal (43 IU/L for men, 37 IU/L for women).

Intervention: Adefovir dipivoxil 10 mg orally once daily (n = 80) or placebo (n = 40) for 48 weeks.

Outcomes: Change in serum HBV DNA and ALT levels, proportions of patients with undetectable HBV DNA (< 1000 copies/mL) and ALT levels in the normal range, and side effects.

Patient follow-up: 90% (intention-to-treat analysis).

MAIN RESULTS

{Serum HBV DNA and ALT levels were decreased from baseline after the first 48 weeks of treatment with adefovir.}† At the end of the second 48 weeks, the decreased levels were maintained in the adefovir group, but not in the placebo group (Table), in which reversion to near-baseline values occurred within 4 to 8 weeks of switching to placebo. More patients had undetectable HBV DNA and ALT levels in the normal range in the adefovir group than in the placebo group (Table). In the adefovir group, HBsAg seroconversion occurred in 1 patient (1.3%), and 4 patients (5.1%) developed resistance mutations. Adverse events were similar in the 2 groups.

CONCLUSION

In patients with HBeAg-negative chronic hepatitis B, the benefits of adefovir dipivoxil did not persist after discontinuation of treatment.

Source of funding: Gilead Sciences.

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*See Glossary.

†**Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al.** N Engl J Med. 2003;348:800-7.

Adefovir dipivoxil vs placebo following treatment with adefovir for hepatitis B e antigen–negative chronic hepatitis B at 48 weeks‡

Outcomes	Adefovir (baseline)	Placebo (baseline)	Difference in medians	*P* value
Change in HBV DNA (log copies/mL) (median)	–3.5 (7.1)	–1.1 (7.2)	–2.4	<0.001
Change in ALT (IU/L) (median)	–59 (98)	–30 (86)	–29	0.01
			RBI (95% CI)	NNT (CI)
Patients with undetectable HBV DNA	71%	8%	805% (239 to 2546)	2 (2 to 3)
Patients with ALT in normal range	73%	32%	133% (49 to 292)	3 (2 to 5)

‡ALT = alanine aminotransferase; HBV = hepatitis B virus. Other abbreviations defined in Glossary; difference in medians, RBI, NNT, and CI calculated from data in article.

COMMENTARY

Unlike hepatitis C, the therapeutic strategy for chronic hepatitis B remains complex and controversial for the following reasons: the possibility of spontaneous seroconversion; the moderate efficacy of subcutaneous (interferon) or oral (lamivudine or adefovir) drugs; the absence of increased response rate with multitherapies; the emergence of drug-induced viral resistance mutations; and the lack of a single, clinically relevant endpoint for the evaluation of efficacy.

To help with the choice of drug and treatment duration, Hadziyannis and colleagues clearly showed that, in patients with HBeAg-negative chronic hepatitis B, oral adefovir should not be stopped after 1 year of treatment. As previously shown with lamivudine, the high therapeutic benefit achieved with adefovir, in terms of the number of patients with undetectable HBV DNA and normal ALT, disappeared after discontinuation of treatment. Even with a low emergence of resistance mutations, the decision to treat with adefovir means nonstop therapy for many years to avoid viral rebound after withdrawal of treatment.

Given these results, the conclusions of the study by Lau and colleagues are not surprising. The study compared lamivudine alone, peginterferon α-2a alone, or the combination in patients with HBeAg-positive chronic hepatitis B. At the end of the 48-week treatment period, HBV DNA levels were lower in the 2 groups of patients who received lamivudine. However, efficacy was also evaluated 24 weeks after the end of the treatment. At this time, all the therapeutic benefits of lamivudine had disappeared, and the best therapeutic results were observed in the 2 groups of patients who were previously treated with peginterferon.

In summary, such nucleoside analogues as lamivudine have an on-treatment 50% response rate (undetectable HBV DNA in serum, histologic improvement, and normalization of ALT) but are associated with a high emergence of resistance mutations (1). Adefovir, a nucleotide analogue, offers a similar level of benefit with a lower incidence of resistance but is associated with increased risk for renal toxicity. In cases

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Peginterferon α-2a alone or with lamivudine increased response rates more than lamivudine alone for HBeAg-positive chronic hepatitis B

Lau GK, Piratvisuth T, Luo KX, et al. **Peginterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B.** N Engl J Med. 2005;352:2682-95.

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

QUESTION

In patients with hepatitis B e antigen (HBeAg)–positive chronic hepatitis B, is peginterferon α-2a, with or without lamivudine, more effective than lamivudine alone?

METHODS

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

Allocation: Concealed.*

Blinding: Blinded (clinicians and patients) (to use of lamivudine or placebo in peginterferon α-2a groups only).*

Follow-up period: 72 weeks.

Setting: 67 sites in 16 countries.

Patients: 814 patients (mean age 32 y, 78% men) who had been positive for hepatitis B surface antigen (HBsAg) for ≥ 6 months; were negative for antibodies to HBsAg and positive for HBeAg; and had hepatitis B virus (HBV) DNA level > 5×10^5 copies/mL, serum alanine aminotransferase (ALT) level > 1 but ≤ 10 times the upper limit of normal, and findings on liver biopsy in the previous 12 months consistent with chronic hepatitis B. Exclusion criteria included decompensated liver disease, neutrophil count < 1500/mm^3, platelet count < 90 000/mm^3, serum creatine level > 1.5 times the upper limit of normal, and infection with hepatitis C or D virus or HIV.

Intervention: Peginterferon α-2a, 180 μg injected once weekly, plus oral placebo once daily (n = 271); peginterferon α-2a, 180 μg once weekly, plus lamivudine, 100 mg orally once daily (n = 271); or lamivudine, 100 mg once daily (n = 272) for 48 weeks. Allocation was stratified by region and ALT level.

Outcomes: HBeAg seroconversion, suppression of HBV DNA levels to < 10^5 copies/mL, combined response (HBeAg seroconversion, suppression of HBV DNA, and normalization of ALT), and adverse events.

Patient follow-up: {90%}† (all patients included in the intention-to-treat analysis; patients with missing values at the end of follow-up were analyzed as having no response).

MAIN RESULTS

At 24 weeks after stopping treatment, patients who received peginterferon α-2a, alone or plus lamivudine, had higher rates of HBeAg seroconversion, suppression of HBV DNA levels, and combined response than did those who received lamivudine monotherapy (Table). Adverse event rates, especially pyrexia, fatigue, headache, and myalgia, were higher in the 2 peginterferon α-2a groups than in the lamivudine-alone group (89% vs 56%, P < 0.001).

CONCLUSIONS

In patients with HBeAg-positive chronic hepatitis B, peginterferon α-2a, with or without lamivudine, increased rates of sustained HBeAg seroconversion and suppression of HBV DNA levels to < 100 000 copies/mL more than lamivudine alone. However, risk for adverse events was increased.

Source of funding: Roche.

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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–positive chronic hepatitis B at 72 weeks‡

Outcomes	Comparisons	Event rates	RBI (95% CI)	NNT (CI)
HBeAg seroconversion	P vs L	32% vs 19%	68% (25 to 127)	8 (5 to 18)
	P + L vs L	27% vs 19%	43% (4.8 to 95)	13 (7 to 92)
HBV DNA < 10^5 copies/mL	P vs L	32% vs 22%	44% (8.6 to 91)	11 (6 to 45)
	P + L vs L	34% vs 22%	52% (15 to 102)	9 (6 to 25)
Combined response	P vs L	23% vs 10%	122% (48 to 236)	8 (6 to 16)
	P + L vs L	21% vs 10%	101% (32 to 206)	10 (7 to 23)

‡HBeAg = hepatitis B e antigen; HBV = hepatitis B virus. Other abbreviations defined in Glossary; RBI, NNT, and CI calculated from data in article.

COMMENTARY

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with viral resistance to lamivudine, a switch to adefovir might be possible with an overlap treatment period of a few months.

The major problem with lamivudine and adefovir is the high rate of relapse when treatment is discontinued. Peginterferon provides a lower response rate and has many well-known side effects, but sustained suppression of HBV DNA is more frequent, and treatment can be stopped at the end of the 24- or 48-week treatment period without risk for relapse or resistance mutation. Furthermore, peginterferon, but not lamivudine alone, is able to induce HBsAg seroconversion in a small proportion of patients (3% in the Lau study).

In the absence of evidence-based, worldwide recommendations, which therapeutic strategy should reasonably be proposed (2)? First, treatment is indicated only in patients with histologically proven chronic HBsAg-positive hepatitis with high levels of HBV DNA and elevated ALT. Second, if the patient agrees to the constraints of this treatment, peginterferon might be the first therapeutic proposition for a 48-week treatment period. Even if this drug offers a low response rate, it can be stopped without preventing the use of a second-line oral treatment. Third, if treatment with peginterferon fails or is refused, oral nucleoside or nucleotide analogues should be prescribed. However, this treatment has a suboptimal antiviral effect and it may have to be administered indefinitely. Combination therapy does not improve clinical response. The therapeutic strategy for hepatitis B is now becoming clearer, but to improve the efficacy of treatment, studies with longer follow-up and more potent new drugs are needed.

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