

in Pregnant Women (ACHOIS) trial was designed to assess whether treatment of gestational diabetes improved health outcomes; it was not designed as a screening trial. Populations vary as to the prevalence of pregnant women who will have gestational diabetes mellitus; hence the number needed to screen will need to be calculated for local populations.

Caroline A. Crowther, F.R.A.N.Z.C.O.G.  
Janet E. Hiller, Ph.D.  
Jeffrey S. Robinson, F.R.A.N.Z.C.O.G.  
University of Adelaide  
Adelaide, SA 5005, Australia  
for the ACHOIS Trial Group

## Treatment of HBeAg-Positive Hepatitis B with Peginterferon and Lamivudine

**TO THE EDITOR:** Lau et al. (June 30 issue)<sup>1</sup> studied pegylated interferon for the treatment of hepatitis B e antigen (HBeAg)-positive chronic hepatitis B. Overall, HBeAg seroconversion was highest among patients treated with pegylated interferon monotherapy, despite the more potent hepatitis B virus (HBV) DNA suppression with lamivudine at 48 weeks. Although viral suppression and HBeAg seroconversion are well correlated,<sup>2</sup> the degree of viral suppression needed for seroconversion to occur is not well defined. With regard to this study, it would be of interest to know what the degree of HBV DNA suppression was among patients in whom HBeAg or hepatitis B surface antigen seroconversion occurred, as a separate analysis. Knowledge of statistically significant predictors of seroconversion at 48 weeks and at 72 weeks would also be relevant. In addition, the characteristics of patients in whom seroreversion occurred between week 48 and week 72 would be important to know.

With regard to tolerance of pegylated interferon, nearly half the patients required dose modification. Since HBeAg seroconversion is known to occur with pegylated interferon at lower doses,<sup>3</sup> it would be helpful if Lau et al. would comment on any effects of dose modification on seroconversion rates, HBV DNA levels, or both.

Kenneth Song, M.D.

Pankaj Rajvanshi, M.D.

University of Washington  
Seattle, WA 98195  
kenneths@u.washington.edu

1. 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.

2. Mommeja-Marin H, Mondou E, Blum MR, Rousseau F. Serum HBV DNA as a marker of efficacy during therapy for chronic HBV infection: analysis and review of the literature. *Hepatology* 2003;37:1309-19.

3. Janssen HL, van Zonneveld M, Senturk H, et al. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. *Lancet* 2005;365:123-9.

**TO THE EDITOR:** The comparison made by Lau et al. between peginterferon alfa-2a and lamivudine monotherapy administered for a fixed time period of 48 weeks, regardless of the occurrence and moment of seroconversion, does not make much sense. Current guidelines recommend administration of lamivudine for a minimum of one year and maintenance treatment for three to six months after HBeAg seroconversion is confirmed, on two occasions that are at least two months apart, in order to reduce the rates of relapse after treatment and potentially life-threatening flares.<sup>1</sup> The duration of treatment reported in this trial is therefore suboptimal for the majority of patients treated with lamivudine. It would have been more appropriate to continue lamivudine in patients who did not meet the criteria of current guidelines at week 48.

Hans Orlent, M.D.

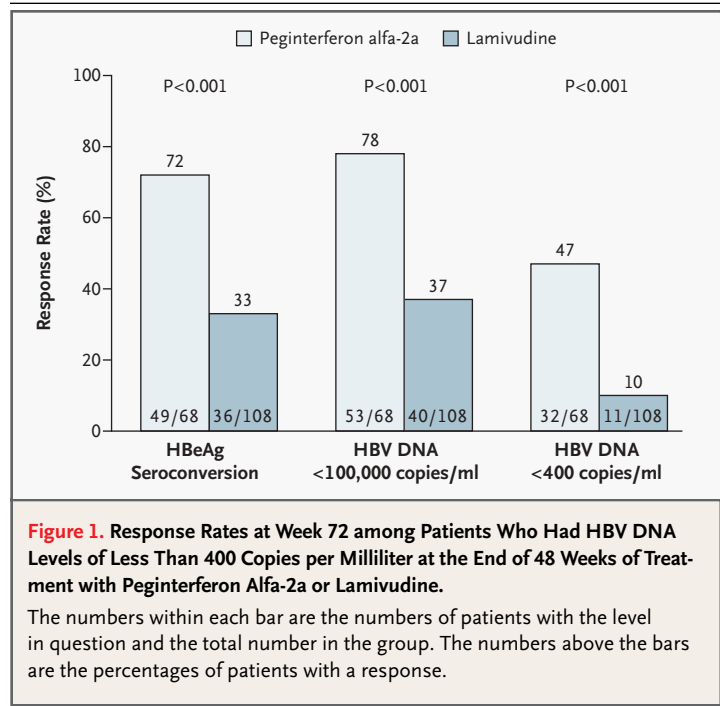
Algemeen Ziekenhuis Sint Jan Hospital  
8000 Brugge, Belgium  
hans.orient@azbrugge.be

1. Lok AS, McMahon BJ. Chronic hepatitis B: update of recommendations. *Hepatology* 2004;39:857-61.

**THE AUTHOR REPLIES:** As noted by Drs. Song and Rajvanshi, viral suppression has been correlated with HBeAg seroconversion. Among patients receiving peginterferon alfa-2a monotherapy in our study, the mean HBV DNA levels were reduced by 5.3 log copies between baseline and 24 weeks after treatment (week 72 overall) among patients with HBeAg seroconversion as compared with 0.8 log copies among patients without seroconversion. However,

response rates at week 72 were significantly higher with peginterferon alfa-2a than with lamivudine among patients who had identical HBV DNA levels at the end of the 48-week treatment period (Fig. 1). This result suggests that the immunomodulatory activity of peginterferon alfa-2a plays an important role in improving sustained responses as compared with lamivudine. For all treatment groups, multivariate analysis identified baseline levels of alanine aminotransferase, HBV DNA, and HBeAg as significant predictors of HBeAg seroconversion at week 72. Despite the high number of dose modifications reported, 78 percent of the patients treated with peginterferon alfa-2a monotherapy received 90 percent or more of the total dose. The rates of HBeAg seroconversion were 28 percent and 33 percent among patients receiving less than 90 percent and 90 percent or more of the total dose, respectively.<sup>1</sup>

Although Dr. Orlent's comments on current recommendations for lamivudine treatment are accurate, insurance policies in some parts of the world where the study was conducted still support only a limited duration of lamivudine treatment (Liaw YF: personal communication). This has highlighted the clinical problems associated with stopping lamivudine, such as seroreversion, virologic relapse, alanine aminotransferase flares, and even hepatic decompensation, which are of major concern when nucleoside or nucleotide analogue therapy is used for the treatment of chronic hepatitis B.<sup>2,3</sup> Even with prolonged lamivudine therapy, the rates of HBeAg seroconversion increase by only 1 to 7 percent per year after the first year of treatment,<sup>4</sup> which is in line with the spontaneous seroconversion rate. Only after five years of lamivudine treatment did the rates of HBeAg seroconversion reach levels (35 percent)<sup>4</sup> that compare favorably with those achieved in our study after one year of peginterferon alfa-2a treatment and six months of follow-up (32 percent). Moreover, prolonged therapy with lamivudine will increase the incidence of resistance to lamivudine related to mutations of the tyrosine, methionine, aspartate, and aspartate motif, which is associated with potentially life-threatening disease exacerbations.<sup>5</sup>



George K.K. Lau, M.D.

University of Hong Kong  
Hong Kong, China  
gkklau@netvigator.com

for the Peginterferon Alfa-2a HBeAg-Positive  
Chronic Hepatitis B Study Group

1. Lau GKK, Piratvisuth T, Luo KX, et al. Peginterferon alfa-2a (40KD) (PEGASYS) qw versus peginterferon alfa-2a plus lamivudine versus lamivudine in HBeAg-positive chronic HBV: effect of previous treatment and drug exposure on sustained response. *J Hepatol* 2005;42:Suppl 1:15. abstract.
2. Epivir-HBV (lamivudine): U.S. prescribing information. Rev. ed. December 2004. (Accessed September 22, 2005, at [http://us.gsk.com/products/assets/us\\_epivir\\_hbv.pdf](http://us.gsk.com/products/assets/us_epivir_hbv.pdf).)
3. Liaw YF, Leung N, Guan R, et al. Asian-Pacific Consensus statement on the management of chronic hepatitis B: a 2005 update. *Liver Int* 2005;25:472-89.
4. Lo GH, Lai KH. Is it meaningful to pursue the safety of long-term lamivudine treatment in patients with chronic hepatitis B? *Gastroenterology* 2004;126:1932-3.
5. Liaw YF, Chien RN, Yeh CT, Tsai SL, Chu CM. Acute exacerbation and hepatitis B virus clearance after emergence of YMDD motif mutation during lamivudine therapy. *Hepatology* 1999;30:567-72.