Should Antiviral Treatment Be Extended to Patients with Chronic Hepatitis B and Mildly Elevated Alanine Aminotransferase?

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The availability of seven approved therapies, including five oral drugs, for chronic hepatitis B has expanded the indications for treatment. The decision to initiate treatment is easy in patients with liver failure, but there continues to be debate regarding when treatment should be initiated in patients with precirrhotic liver disease.[1,2] Recognizing that liver biopsy is not performed on all patients with chronic hepatitis B, the guidelines of the American Association for the Study of Liver Diseases (AASLD)[3,4] and the Asian Pacific Association for the Study of the Liver (APASL)[5] primarily rely on alanine aminotransferase (ALT) levels to guide treatment decisions. The AASLD and APASL guidelines recommend treatment for patients with an ALT level higher than 2 times the upper limit of normal (ULN) range and liver biopsy to guide treatment decisions for patients with an ALT level 1 to 2 times ULN, particularly if they are above the age of 40 years. The guidelines of the European Association for the Study of the Liver place more emphasis on liver histology; they recommend treatment for patients with at least a Metavir activity grade of A2 (range = 0-3) or a Metavir fibrosis score of F2 (range = 0-4).[6] All three guidelines recommend that patients who are deemed not to be treatment candidates at presentation be monitored so that treatment can be initiated later when the liver disease becomes more active.

Many investigators have challenged the recommendation to defer treatment in patients with normal or mildly elevated ALT levels. These experts cite recent studies finding that up to 50% of hepatitis B carriers with normal levels of ALT may have histologically significant liver disease; however, many of the studies involved small numbers of patients, most studies monitored ALT on only one or two occasions over a 6-month period prior to biopsy, and all but one study failed to report the number of patients with normal levels of ALT that were not biopsied. Thus, the findings of these studies may not be generalized to patients with persistently normal levels of ALT. For example, Kumar et al.[7] reported that 21% of hepatitis B e antigen (HBeAg)–negative patients with persistently normal ALT levels and hepatitis B virus (HBV) DNA levels below 5 $\log_{10}$ copies/mL had histologically active liver disease, but only 29 of 75 patients (39%) who met the ALT and HBV DNA criteria underwent liver biopsy. Furthermore, the conclusion that a fair proportion of "inactive carriers" had histologically significant liver disease was based on the findings of six patients who had a maximum fibrosis score of 1 (in a range of 0-4) and a maximum histology activity index of 5 (in a range of 0-18). In another study, 59 patients who had normal levels of ALT on at least two occasions 6 months apart underwent liver biopsy; 18% had significant fibrosis (Metavir score $\geq$ F2), and 34% had significant inflammation (Metavir score $\geq$ A2).[8] It should be noted that only patients with HBV DNA levels $>$ 4 $\log_{10}$ copies/mL were biopsied, and age $>$ 40 years was an important predictor of significant liver disease. In a third study, 24 of 69 patients (35%) with ALT levels 1 to 2 times ULN had significant liver disease as defined by a fibrosis stage $\geq$ 2 (range = 0-4) or fibrosis stage 1 and an inflammation grade $\geq$ 2 (range = 0-4).[9] Age $>$ 35 years, male gender, and increasing ALT levels were predictors of significant liver disease.

Studies that have focused on patients in the immune-tolerant phase have shown that hepatic inflammation and fibrosis are negligible to mild in most patients with minimal or no progression after 5 years. In one study of 40 patients, 20 had a Metavir fibrosis score of F0, and 20 had a score of F1; 9 had a Metavir activity score of A0, 29 had a score of A1, and only 2 had a score of A2.[10] In another study of 57 patients, 19 had an Ishak fibrosis score of 0 (range = 0-6), and 38 had stage 1 fibrosis.[11] Follow-up biopsies after a mean of 5 years revealed no changes in the fibrosis scores for 42 of 48 patients who remained in the immune-tolerant phase.

These findings indicate that significant liver disease can be found in HBV carriers with normal ALT levels, but the

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; APASL, Asian Pacific Association for the Study of the Liver; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; ULN, upper limit of normal.

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likelihood is low in those with persistently normal ALT levels, particularly if they are younger than 35 or 40 years or have serum HBV DNA levels below 4 $\log_{10}$ copies/mL.

In this issue of HEPATOLOGY, Wu et al.[12] report a retrospective analysis of the liver histology and treatment response in a subset of patients who participated in the phase III clinical trials of entecavir in nucleoside-naïve patients with chronic hepatitis B. All the patients had at least one ALT measurement 1.3 to 10 times ULN during the 12 weeks prior to screening, an ALT measurement 1.3 to 2 times ULN at screening and at the baseline visit, and a liver biopsy with findings of chronic hepatitis. A total of 336 patients (190 HBeAg-positive patients and 146 HBeAg-negative patients), comprising 25% of the study population, met these criteria. They found that clinically significant necroinflammation, defined as a Knodell necroinflammatory score ≥ 7 (range = 0-18), was present in 60% of HBeAg-positive patients and in 72% of HBeAg-negative patients, and marked fibrosis, defined as an Ishak fibrosis score ≥ 4 (range = 0-6), was observed in 8% of HBeAg-positive patients and in 15% of HBeAg-negative patients. The high percentage of patients with "mildly elevated ALT at baseline" who had significant necroinflammation or marked fibrosis is surprising and is likely related to the criteria used for selecting this subset of patients. Thus, these patients not only had ALT levels 1.3 to 2 times ULN on two occasions (the screening and baseline visits), but they also had at least one ALT measurement 1.3 to 10 times ULN prior to screening and an HBV DNA level $>$ 3,000,000 Eq/mL (for HBeAg-positive patients) or $>$ 700,000 Eq/mL (for HBeAg-negative patients). Because of discrepancies in the Results and Discussion sections, it is unclear how many of these patients had ALT levels 1.3 to 2 times ULN and how many had ALT levels 2 to 10 times ULN prior to screening. Of greater importance is the requirement for evidence of chronic hepatitis on liver biopsy as an entry criterion for these trials. This criterion was necessary because the primary efficacy endpoint of these trials was histological response (defined as an improvement in the Knodell necroinflammatory score of at least 2 points and no worsening of the fibrosis score). It is not clear how many patients with ALT levels 1.3 to 2 times ULN at screening were excluded because of a "low" necroinflammatory score on baseline biopsy that would have precluded an assessment of histological response. Therefore, the finding that a high percentage of patients with mildly elevated ALT levels have significant liver disease on biopsy cannot be generalized to other patients with ALT levels 1.3 to 2 times ULN on one occasion or ALT levels persistently within 1.3 to 2 times ULN during follow-up or to patients with lower HBV DNA levels.

Wu et al.[12] noted that, compared to patients with baseline ALT levels $>$ 2 times ULN, HBeAg-negative patients with baseline ALT levels 1.3 to 2 times ULN who received entecavir had slightly lower rates of histological improvement (66% versus 72%), HBV DNA suppression (86% versus 91%), and ALT normalization (76% versus 78%) at week 48, but these differences were not significant. By contrast, HBeAg-positive patients with baseline ALT levels 1.3 to 2 times ULN who received entecavir had significantly lower rates of all responses at week 48 in comparison with those with baseline ALT levels $>$ 2 times ULN: 62% histological improvement versus 75% ($P = 0.001$), 48% HBV DNA suppression versus 73% ($P < 0.001$), 55% ALT normalization versus 73% ($P = 0.001$), and 8% HBeAg seroconversion versus 26% ($P < 0.001$).

These data extend the results of previous studies showing that both interferon and nucleos(t)ide analogues are less efficacious in patients who are in the immune-tolerant phase[13] and support the recommendations that HBeAg-positive patients with ALT levels 1 to 2 times ULN should be monitored and that those with ALT levels persistently in this range should undergo liver biopsy to guide treatment decisions. Although Wu et al.[12] showed that antiviral therapy can result in viral suppression and histological improvement, responses were assessed at week 48 while the patients were undergoing treatment. Long-term (multiyear and possibly lifelong) treatment will be necessary for many of these patients to maintain the responses. Therefore, until data supporting a benefit of antiviral therapy for clinical outcomes become available, initiating every chronic hepatitis B patient with mildly elevated ALT levels is not warranted. Some of these patients will turn out to have mild liver disease on biopsy, and others, notably young HBeAg-positive patients, may undergo spontaneous HBeAg seroconversion and enter into remission (at least temporarily) during the next few years.

As our knowledge about the natural history of chronic HBV infection improves and new and better treatments become available, it is appropriate to regularly review the indications for treatment. The Hepatitis B Research Network, sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, will be conducting clinical trials in patients with mild liver disease. Until data from these trials become available, the decision to initiate treatment in chronic hepatitis B patients with mildly elevated ALT levels should be individualized.

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