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Editorial

Is liver biopsy necessary to indicate antiviral therapy in patients with chronic HBV infection?

It is estimated that some 400 million people are infected with HBV worldwide, and around 20% of these may die prematurely from serious complications such as hepatocellular cancer or decompensated liver cirrhosis. In Spain, the prevalence may have increased in the last decade because of immigrants from high-prevalence countries. Patients needing therapy should be identified and kept with negative viral loads using novel antiviral drugs in order to change the natural history of this condition and avoid complications.

Two transmission mechanisms stand out in the natural history of this disease: a) vertical transmission from mothers to newborns, who are easily infected depending on the mother's viral load. Infection becomes chronic in over 90% of cases with a prolonged immunotolerance stage characterized by normal ALT, high viral load, HBeAg-positive and few or no liver lesions; and b) interpersonal transmission in adolescents and adults with a short or non-existent immunotolerance stage. Fewer than 5% become chronic and are characterized by an immune reaction phase: increased ALT and lower viral load is chronic HBeAg-positive hepatitis. In addition, children, after a prolonged immunotolerance stage, develop immune reactivity between the second and fourth decades of life. During this phase, seroconversion to anti-HBe is initiated, which involves a resolution of viral activity. Nevertheless, some patients keep high HBV DNA levels and increased ALT (chronic anti-HBe-positive or HBeAg-negative hepatitis, reactivation phase). At best, the disease evolves towards a resolution of viral activity in inactive carriers: persistent normal ALT levels, HBV-DNA below 2000 IU/ml, and minimal liver lesions or normal liver except when there was cirrhosis previously. The inactive carrier status may be reversible and return an HBeAg-positive or -negative immunoreactivity stage (1). True healing occurs when HBsAg disappears, which is not always associated with seroconversion to anti-HBs status – the ideal outcome. In addition, complete HBV eradication is not achieved either spontaneously or with therapy since cccDNA is not cleared from liver cells. HBsAg negativization occurs spontaneously in only 0.5% to 1% yearly. Recently, in a follow-up of 3087 HBsAg-positive individuals (REVEAL study) in Taiwan for 8 years a yearly clearance rate of 2.26% was reported (2). With antiviral therapy, HBsAg elimination at 2 years is lower than 3-5%.

A most important issue is telling patients with chronic anti-HBe-positive hepatitis with a low viral load – even lower than 2000 IU/ml – and normal or nearly normal ALT from inactive carriers. ALT is known to fluctuate in the former with prolonged periods of normal ALT (45-65%), whereas ALT remains normal

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in the latter and their viral load remains below 2000 IU/ml. Overall, in the study of HBV several annual checkups are needed to gain insight into actual patient status. In contrast to HCV, for which just one follow-up suffices in checking patient clinical status, HBV needs a more in-depth study with several ALT and viral load measurements to reveal disease stage. Also, plasma HBsAg determination may help differentiate both situations; for inactive carriers HBsAg levels lower than 1000 IU/mL plus HBV DNA inferior to 2000 IU/ml has a diagnostic sensitivity of 91% and a specificity of 95% (3).

According to clinical guidelines (4,5), patients during immunotolerance and inactive carriers should receive no therapy, which is indicated during the immune reactive stage alone. It is thought that treatment may be initiated with viral load, with no consideration to factors such as ALT or liver biopsy. This is based on the close relationship between HBV DNA levels and liver cirrhosis or hepatocellular carcinoma. Nevertheless, the decision to treat a patient – except for urgent management indications – should be made bearing all three factors in mind. Initially we should assess ALT and HBV DNA on more than one occasion for at least 6 months, and then – when necessary – a liver biopsy should be performed. It is important that patients should be treated with no haste – HBeAg-positive subjects younger than 40 years the course of disease may be benign, and some even exhibit spontaneous seroconversion to anti-HBe. This suggests that, depending on the actual case, an HBeAg-positive patient younger than 30 or 40 years needs no immediate treatment and may simply be monitored. However, should ALT elevation and liver necroinflammatory activity persist after that age, treatment should be administered. A recent study assessed the outcome of HBeAg-positive patients by age at seroconversion to anti-HBe. Patients who seroconverted before 30 years are less likely to develop chronic anti-HBe-positive hepatitis, and more importantly cirrhosis, than those seroconverting at 30 to 40 years of age, and particularly after 40. Therefore, there is an age limit for HBeAg-positive patients, around 30 years, where serious issues derived from chronic infection are uncommon and spontaneous seroconversion may be expected (6). In contrast, anti-HBe-positive patients usually are older and only rarely get better spontaneously, which means that delaying therapy – if indicated – serves no purpose.

It is generally accepted that ALT levels are markers for advanced liver lesion, and antiviral therapy is indicated for patients with ALT above twice the upper limit of normal (ULN) and viral load over 20,000 IU/ml for HBeAg-positive (2000 IU/ml in the European guidelines) and 2000 IU/ml for anti-HBe-positive subjects. If ALT is 1-2 x ULN therapy should be provided for subjects where liver biopsy shows significant necroinflammatory activity and fibrosis, at least twice A2 and F2 according to METAVIR. While ALT may differentiate patients with significant histological lesions, severe liver lesions have been reported in patients with normal ALT. Nevertheless, the number of patients included in most studies is small, ALT was not permanently normal, or viral load was above the acceptable limit (> 2000 IU/ml). In a study of 116 anti-HBe-positive patients with permanently normal ALT, 21% were seen to have fibrosis > 2; however, viral load (HBV DNA < 5 log copies/ml) exceeds limits established for inactive carriers (7). Also in 35 inactive carriers who were anti-HBe-positive and had normal ALT, was fibrosis > 2 seen in 17%, but viral load oscillated between 2000 and 20,000 IU/ml (8). Anyway, a reduction of the normal cut-off for ALT is now

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being assessed, and the suggested upper limit should be 30 U/l for men and 19 U/l for women.

Therefore, liver biopsy plays a crucial role when deciding therapy for these patients. In this issue, Esther Molina-Pérez et al. (9) discuss the importance of liver biopsy in patients with chronic hepatitis and moderate or intermittent ALT increase, as they are most controversial when it comes to deciding their therapy. They include 89 patients – 33 HBeAg-positive and 56 anti-HBe-positive. ALT levels and viral load were measured every three months for one year, and liver biopsy was indicated for those exhibiting intermittent or persistent ALT increases above the ULN and/or HBV DNA > 2000 IU/ml in anti-HBe-positive patients. Immunotolerant patients and inactive carriers were excluded from the study. The most relevant conclusion is that a high number of patients, 60.7%, had liver lesions relevant enough for therapy indication. The indication of liver biopsy was made regardless of viral load or serum markers. Finally, if ALT was normal at liver biopsy indication, 47.1% had therapy indication versus 69.1% when ALT was increased (P = 0.04). Probably, the former group was more prone to periods with normal ALT as compared to the latter, which may influence liver lesion extent. In the study by Kumar et al. (7), with a very high number of patients, approximately 65% had fibrosis ≥ 2. Lastly, according to Papatheodoridis et al. (8) in anti-HBe-positive patients, 91% with HBV DNA > 200,000 IU/ml have therapy indicated depending on histology, and 75% should viral load oscillate between 2000 and 20,000 IU/ml. Similarly, in patients with persistently elevated ALT, 86% had therapy indicated versus 74% when ALT increases are transient.

Liver biopsy has not been replaced yet; for HBV the most significant indication is antiviral therapy assessment, especially in subjects with ALT below twice the ULN. Alternative methods, including elastography, have not been validated. Therefore, we should first make a diagnosis as accurate as feasible, and most importantly differentiate true inactive markers from immunoreactive, anti-HBe-positive patients. Then, in the group with ALT at 1-2 x ULN, the study of viral load together with ALT in repeated measurements is important but insufficient, and the workup should be completed with a liver biopsy to allow for an accurate therapy indication.

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