Research Article
Viral Hepatitis

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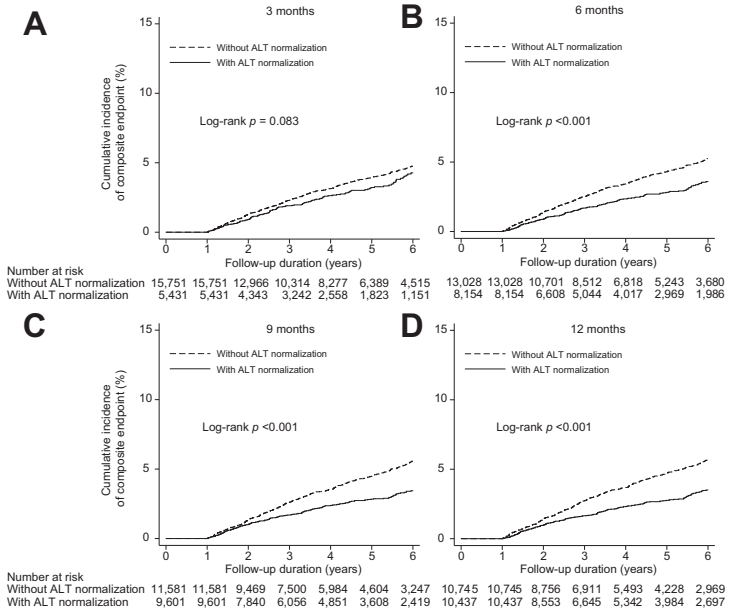
Normal on-treatment ALT during antiviral treatment is associated with a lower risk of hepatic events in patients with chronic hepatitis B

Graphical abstract



- 21,182 CHB patients (10,437 normal and 10,745 elevated on-treatment ALT at 12 months after antiviral treatment) were identified and followed for 4.0 ± 1.7 years.
- Patients normal and elevated on-treatment ALT differed in baseline ALT (58 *vs.* 61 U/L), HBV DNA (4.9 *vs.* 5.1 $\log_{10}$ IU/ml) and cirrhosis status (8.8% *vs.* 10.5%).
- 627 (3.0%) patients developed composite hepatic events. Compared to elevated on-treatment ALT, normal ontreatment ALT at 3, 6, 9 and 12 months reduced the risk of hepatic events, after adjustment for baseline ALT and other important co-variates, with adjusted hazard ratios (95% CI) of 0.61 (0.48-0.76), 0.54 (0.44-0.66), 0.53 (0.44-0.64) and 0.50 (0.42-0.61) respectively (all p <0.001).
- The cumulative incidence (95% CI) of composite hepatic events at 6 years was 3.51% (3.06%-4.02%) in normal on treatment and 5.70% (5.15%-6.32%) in elevated on treatment ALT (p <0.001).

Highlights

- Patients with normal on-treatment ALT after antiviral treatment had lower risk of hepatic events.
- Adjusted hazard ratios for normal on-treatment ALT at 3, 6, 9 and 12 months were 0.61, 0.54, 0.53 and 0.50 respectively.
- Similar findings were identified using AASLD, APASL or local laboratory criteria for normal ALT.

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Lay summary

We investigated 21,182 patients with chronic hepatitis B receiving antiviral treatment. Alanine aminotransferase is a laboratory marker of liver function, with raised levels indicating liver dysfunction and in severe cases hepatitis. Normal on-treatment alanine aminotransferase during the first year of treatment in patients with CHB is associated with a lower risk of hepatic events.

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Normal on-treatment ALT during antiviral treatment is associated with a lower risk of hepatic events in patients with chronic hepatitis B

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Background & Aims: Recent studies reveal that the rate of normal on-treatment alanine aminotransferase (ALT) appears different for different nucleos(t)ide analogues (NAs); yet its clinical significance is unclear. We aimed to evaluate the impact of normal on-treatment ALT during antiviral treatment with entecavir (ETV) or tenofovir disoproxil fumarate (TDF) in patients with chronic hepatitis B (CHB).

Methods: A territory-wide cohort of patients with CHB who received ETV and/or TDF in 2005–2016 was identified. Serial on-treatment ALT levels were collected and analyzed. Normal on-treatment ALT (ALT-N) was defined as ALT <30 U/L in males and <19 U/L in females. The primary and secondary outcomes were composite hepatic events (including hepatocellular carcinoma) based on diagnostic codes. Patients with hepatic events before or during the first year of antiviral treatment or follow-up <1 year were excluded.

Results: A total of 21,182 patients with CHB (10,437 with and 10,745 without ALT-N at 12 months after antiviral treatment) were identified and followed for 4.0 ± 1.7 years. Patients with and without ALT-N differed in baseline ALT (58 *vs.* 61 U/L), hepatitis B virus DNA (4.9 *vs.* 5.1 log10 IU/ml) and cirrhosis status (8.8% *vs.* 10.5%). A total of 627 (3.0%) patients developed composite hepatic events. Compared to no ALT-N, ALT-N at 3, 6, 9 and 12 months reduced the risk of hepatic events, after adjustment for baseline ALT and other important covariates, with adjusted hazard ratios (95% CI) of 0.61 (0.49–0.77), 0.55 (0.45–0.67), 0.54 (0.44–0.65) and 0.51 (0.42–0.61) respectively (all p <0.001). The cumulative incidence (95% CI) of composite hepatic events at six years was 3.51% (3.06%-4.02%) in ALT-N and 5.70% (5.15%–6.32%) in the no ALT-N group (p <0.001).

Conclusions: Normal on-treatment ALT is associated with a lower risk of hepatic events in patients with CHB receiving NA treatment, translating into improved clinical outcomes in these patients.

Lay summary: We investigated 21,182 patients with chronic hepatitis B receiving antiviral treatment. Alanine aminotransferase is a laboratory marker of liver function, with raised levels indicating liver dysfunction and in severe cases hepatitis. Normal on-treatment alanine aminotransferase during the first year of treatment in patients with CHB is associated with a lower risk of hepatic events.

Introduction

Elevated alanine aminotransferase (ALT) above two times the upper limit of normal (ULN) in patients with chronic hepatitis B (CHB) is one of the key indications for antiviral treatment recommended by international guidelines.[1–3] Normal on-treatment ALT is often regarded as a biochemical response to antiviral treatment. Being one of the most commonly used tests for patients with CHB, ALT level correlates with hepatic necroinflammation.[4] The optimal ALT cutoffs are now set at 30 IU/L for men and 19 IU/L for women by the American Association for the Study of Liver Diseases (AASLD),[3] as high-normal ALT levels according to traditional cutoffs ranging from 40 U/L to 70 U/L are also associated with cirrhosis[5] and liver-related mortality.[6]

Recent studies showed that patients receiving tenofovir alafenamide (TAF) are more likely to achieve normal on-treatment ALT than those receiving tenofovir disoproxil fumarate (TDF) based on AASLD criteria (but not central laboratory criteria), despite a similar rate of viral suppression.[7,8] In pooled analyses and individual trials, normal on-treatment ALT rates by AASLD and central laboratory criteria were significantly higher in TAF than TDF recipients at most assessed time points up to 96 weeks.[9] Yet the exact underlying mechanisms of this observation remain obscured.

In patients receiving first-line nucleos(t)ide analogue (NA) treatment, most of them would have achieved complete viral suppression within 12 months.[7,8,10,11] Even so, up to 58% had elevated on-treatment ALT by AASLD criteria at two years.[12] Persistently elevated ALT in patients with complete viral suppression may imply the co-existence of fatty liver,[13] and was associated with a lower likelihood of cirrhosis regression in patients treated with TDF for five years.[10] Nonetheless, whether early normal on-treatment ALT confers better clinical outcomes is yet to be proven, as most studies only considered baseline

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