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Prospective evaluation of ethnicity and HBV genotype in predicting off-treatment outcomes after nucleos(t)ide analogue cessation: results from the multicentre COIN-B trial

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Background and aims: Determinants of outcomes after nucleos(t)ide analogue (NUC) cessation remain incompletely defined. Ethnicity has been proposed as a stopping criterium, but prospective validation is lacking. We evaluated the impact of ethnicity and HBV genotype (gt) on off-treatment outcomes.
Method: In the multicentre prospective COIN-B trial, start-of-treatment HBeAg-, long-term NUC-suppressed patients without advanced liver fibrosis were followed for 72 weeks after NUC cessation. Recruitment was matched for Caucasian and non-Caucasian ethnicity and stratified by sex and age. The primary endpoint was off-treatment HBV DNA ≤2000 IU/mL + ALT ≤2×ULN at week 72. Ethnicity was defined by country of birth. Ancestry inference was determined using population-specific SNPs. **Results:** Of 91 included patients, 84 completed follow-up (Caucasian: n = 41; non-Caucasian: n = 43). Both groups had comparable end-of-treatment (EOT) quantitative HBsAg levels (p = 1.00). Caucasians were exclusively infected with gt A or gt D, whereas non-Caucasians showed broad gt diversity (A-E). The primary endpoint was reached in 41.5% of Caucasian versus 30.2% of non-Caucasian patients (p = 0.28), and retreatment rates did not differ (31.7% vs 48.8%, p = 0.11). HBsAg loss (7.1%) occurred exclusively in patients of European or North-African/Middle-Eastern ancestry. In multivariate analyses, including either SNP ancestry or gt, lower EOT HBsAg was consistently associated with the primary endpoint, HBsAg loss, and ≥1 log HBsAg decline at week 72, but not retreatment. Compared to European ancestry and adjusted for EOT HBsAg, Asian and Sub-Saharan African ancestries were less likely to have ≥1 log HBsAg decline (OR 0.01, p < 0.001; OR 0.002, p = 0.007), while Asian ancestry was associated with higher retreatment rates (OR 2.83, p < 0.05). Compared to gt A and adjusted for EOT HBsAg, gt C (OR 0.13, p = 0.02) and gt D (OR 0.20, p = 0.009) were less likely to achieve the primary endpoint and more likely to require retreatment (OR 11.9, p = 0.002; OR 3.72, p = 0.03), while gt B (OR 0.01, p = 0.008) and gt C (OR 0.04, p = 0.01) were less likely to have ≥1 log HBsAg decline.
Conclusion: In this prospective ethnicity-matched trial, off-treatment outcomes did not differ between Caucasian and non-Caucasian patients. EOT HBsAg is the dominant predictor of viral control, HBsAg loss and HBsAg decline with differential impacts of ancestry and HBV genotypes. These results call for a more granular definition of ethnicity as stopping criterium.