In the REGENERATE interim analysis, obeticholic acid (OCA) improved liver histology in patients with non-alcoholic steatohepatitis (NASH). Elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels may be associated with fibrosis progression in NASH. We evaluated OCA-mediated improvement in these transaminases, and their utility in monitoring treatment of NASH patients with fibrosis.

REGENERATE NASH patients with stage 2 or 3 fibrosis (N=931) were randomized 1:1:1 to placebo, OCA 10 mg, or OCA 25 mg. Changes in ALT and AST (upper limit of normal [ULN], 55 U/L and 34 U/L, respectively) were analysed. Baseline characteristics were well balanced across groups (mean ± SD): age (55±11 years), ALT (79±53 U/L), AST (58±36 U/L); ALT >ULN, 60% (>3×ULN, 8%); AST >ULN, 73% (>3×ULN, 9%). OCA treatment improved transaminase levels at Month 1 through Month 18. In patients with baseline ALT and AST >ULN, ALT normalized in 36% (placebo), 49% (OCA 10 mg), and 66% (OCA 25 mg), and AST normalized in 28%, 42%, and 49% in the respective groups by Month 18. In patients with normal baseline transaminases, elevations to >ULN were greater for placebo than OCA 10 mg or OCA 25 mg. OCA-mediated improvements in transaminases were greater in patients who achieved the REGENERATE primary endpoints (figure 1).

OCA treatment rapidly improved and sustained ALT and AST, suggesting transaminase may be useful in monitoring treatment response. OCA-treated patients who did not achieve REGENERATE primary endpoints also had marked improvement in transaminases, suggesting longer-term treatment may result in additional histologic improvement.

The UK-PBC Study group validated a long-term prognostic model of primary biliary cholangitis (PBC) that identified independent predictors of end-stage liver disease (ESLD). POISE was a randomized, double-blind (DB), placebo-controlled 12-month Phase 3 trial investigating obeticholic acid (OCA) treatment of PBC; a 5-year open-label extension (OLE) followed. We assessed the change in predicted risk of ESLD with the UK-PBC model in placebo patients (DB phase) who transitioned to OCA (OLE).

POISE inclusion criteria: PBC diagnosis, alkaline phosphatase ≥1.67x upper limit of normal (ULN) and/or total bilirubin >ULN to <2x ULN, stable ursodeoxycholic acid (UDCA) dose or intolerant to UDCA. 73 patients were randomized to placebo; 66 enrolled in the OLE. Baseline, DB month 12, and OLE data through 60 months of OCA treatment were included in the UK-PBC algorithm to assess predicted risk of ESLD at 5, 10, and 15 years.

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The median age at baseline in the placebo group was 55 years; 93% were female, and 93% received daily UDCA (median dose, 15 mg/kg). After 1 year of standard-of-care (SOC), placebo patients demonstrated a slight increase in predicted risk of ESLD (table 1). After 1 year of OCA, predicted risk of ESLD at 5, 10, and 15 years was reduced to below baseline levels; these were sustained through the 60-month OLE.

In POISE, the UK-PBC risk score predicted an increased risk of ESLD in PBC patients treated with SOC and placebo for 12 months. OCA treatment led to sustained reductions in predicted risk of ESLD through 60 months.

The global pooled prevalence of NAFLD is 25% (Youssoufi 2016). Genetic factors have been shown to play a significant role in determining the risk for the development and progression of NAFLD in Caucasian/East Asian populations where robustly replicated associations have been found, many at genome-wide significance, with variants in PNPLA3, TM6SF2, GCKR and HSD17B13, shown to have much lower significance than expected (p value range 1.93 × 10⁻⁶ to 5.83 × 10⁻⁶) including SNPs in chromosome 20 open reading frame 78 (C20orf78), Transmembrane Protein 63C (TMEM63C), Bromodomain Adjacent To Zinc Finger Domain 1A (BAZ1A), Fibroblast Growth Factor 21 (FGF21), and Insulin Receptor Substrate 1 (IRS1). Variants in previously associated loci viz PNPLA3, MBOAT7, TM6SF2, GCKR and HSD17B13, showed much lower significance than expected (p value range 1.20 × 10⁻³ to 0.730).

These findings suggest that there may be divergence in the genetic risk profile for developing NAFLD in the South Asian population compared with European/East Asian populations. This is concordant with the observed divergence in NAFLD phenotype, but needs to be validated in further, larger cohorts.

ND, JC, GM share first authorship. MM, KS, GA share senior authorship.

No associations were identified with NAFLD at genome-wide significance (p < 5 × 10⁻⁸). However, a number of genetic variants implicated in liver-related and metabolic pathology showed suggestive evidence of association (p value range 1.93 × 10⁻⁶ to 5.83 × 10⁻⁶) including SNPs in chromosome 20 open reading frame 78 (C20orf78), Transmembrane Protein 63C (TMEM63C), Bromodomain Adjacent To Zinc Finger Domain 1A (BAZ1A), Fibroblast Growth Factor 21 (FGF21), and Insulin Receptor Substrate 1 (IRS1). Variants in previously associated loci viz PNPLA3, MBOAT7, TM6SF2, GCKR and HSD17B13, showed much lower significance than expected (p value range 1.20 × 10⁻³ to 0.730).

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The Medawar pooled prevalence of NAFLD is 25% (Youssoufi 2016). Genetic factors have been shown to play a significant role in determining the risk for the development and progression of NAFLD in Caucasian/East Asian populations where robustly replicated associations have been found, many at genome-wide significance, with variants in PNPLA3, TM6SF2, MBOAT7, GCKR, and HSD17B13 (Trépo 2020). South Asian patients develop NAFLD and at a lower body mass index (BMI) than their Caucasian counterparts, with reported prevalences of almost 50% among adults in some areas of India (Chalmers 2019). Nevertheless, there has been no systematic attempt, to date, to undertake a genome wide association study (GWAS) of NAFLD in the South Asian community. This study aimed to redress the balance.

The Trivandrum population-based NAFLD cohort comprises of 2222 individuals from Kerala, South India. Genomic DNA was available for 908 participants. Cases were defined as participants who, based on ultrasound scanning, had evidence of fatty infiltration of the liver (n = 454). Controls were defined as participants with no evidence of fatty infiltration (n = 454). Samples were genotyped using the Global Screening Array-24 v3.0 BeadChip (Illumina, Inc), and were imputed against the Haplotype Reference Consortium panel and the population-specific GenomeAsia pilot panel. The analysis was conducted in GMMAT to control for a degree of cryptic relatedness, with the model adjusted for age, sex, and BMI as fixed effects and family structure as a random effect by a relationship matrix calculated in LDHAK.