OBETICHOLIC ACID IMPROVES EXPERIMENTAL NON-INVASIVE MARKERS OF NON-ALCOHOLIC STEATOHEPATITIS AND ADVANCED FIBROSIS: RESULTS OF A SECONDARY ANALYSIS FROM THE MONTH-18 INTERIM ANALYSIS OF THE REGENERATE STUDY

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10.1136/gutjnl-2020-BASL.31

In the REGENERATE 18-month interim analysis, obeticholic acid (OCA) improved surrogate endpoints of liver fibrosis in patients with non-alcoholic steatohepatitis (NASH). New biomarker indices are being developed, including FibroMeter (FM), which is designed to predict fibrosis stage ≥2 using age, gender, alpha-2-macroglobulin, international normalized ratio, platelets, urea, and gamma-glutamyltransferase. FM Vibration-Controlled Transient Elastography (VCTE) uses the same biomarkers (excluding urea) with liver stiffness (LS). The FibroScan AST (FAST™) score uses LS by VCTE, Controlled Attenuation Parameter score, and aspartate aminotransferase to identify patients with NASH and NAFLD Activity Score (NAS) ≥4 and fibrosis stage ≥2.

PATIENT ASSESSMENT AND CHARACTERISTICS IN A SINGLE-CENTRE FONTAN-ASSOCIATED LIVER DISEASE COHORT

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10.1136/gutjnl-2020-BASL.30

Background The Fontan operation is performed in individuals born with a single functional ventricle. The procedure separates venous return from the heart and allows normal arterial oxygen saturations. It extends the life span of these patients, who are now surviving into adulthood. However, the Fontan circulation results in chronic hepatic congestion and reduced portal blood flow. Fontan-associated liver disease (FALD) is an increasingly recognized complication, and can lead to cirrhosis, portal hypertension (PHT) and hepatocellular carcinoma. Screening for liver disease is a critical part of long-term follow-up, although assessment of fibrosis in this cohort is not clear-cut. Here we describe a model for outpatient hepatology review, and report baseline parameters of liver disease in new referrals.

Methods All patients referred to hepatology at the Royal Infirmary of Edinburgh from Dec 2017 to Aug 2019 were included. Demographic data, blood tests and echocardiogram results were recorded in a database at the time of clinic review.

Results 21 patients were included. Mean age was 29 years old, 62% were male. Average age at the time of Fontan completion was 9 years. Median Fontan duration was 20 years (range 8–34). 5/21 patients had evidence of moderate LV impairment. The most common liver enzyme abnormality was isolated raised GGT (87.1 U/l, range 30–326). 20/21 had abdominal ultrasound, 9 had normal liver appearance. Transient elastography (Fibroscan) results were available in 18 patients. Median liver stiffness was 15.4 kPa (range 7.9–34.3). 11/21 patients had clinical features suggestive of possible PHT (varices/ascites/splenomegaly/thrombocytopenia). None of the patients had features of decompensated cirrhosis. Serum bilirubin was higher in patients with features of PHT (29.2 μmol/l vs. 16.9 μmol/l p<0.0167). There was no significant correlation between the presence of features of portal hypertension and liver stiffness or Fontan duration. Serum hyaluronic acid was only mildly elevated in a single patient (mean 35.2, range 20–73) and was not affected by the presence of features of PHT or LV impairment.

Conclusions Individuals with Fontan physiology are surviving longer with the current literature suggesting almost universal development of FALD. Evaluation of FALD is challenging with traditional markers of liver fibrosis being unreliable. We recommend assessment for FALD 10-years post-Fontan including clinical assessment, abdominal ultrasound, laboratory investigations, calculation of fibrosis scores and elastography. Following these individuals over time, and development of a UK registry, would help to improve our understanding of how best to assess fibrosis and predict severity of FALD in unbiased cohorts.

Key to implementation was regular reiteration, evaluation and feedback across the network, utilising Plan, Do, Study, Act (PDSA) cycles to evolve solutions to the needs of each provider and their clients.

We forged a common purpose, combined with a supportive culture to overcome challenges as they emerged. We focused on the positive impacts of our work and the values the nursing team have established to connect and build strong relationships with the staff of our partner organisations.

We focused on a number of areas including training, development, patient and staff needs; working collaboratively to find solutions and establishing working groups where needed. A data dashboard, ‘one version of the truth,’ was shared across all organisations, to inspire discussion about further improvements.

Results Community locations increased from six in 2017–2018 to 17 in 2019–2020 resulting in a five fold increase in the number of patients treated in the community (n=34 vs. n=154) (figure 1). Currently 50% of our HCV treatment is community-based compared to 12% prior to our initiative.

Conclusion Working collaboratively with stakeholders can substantially scale up community-based HCV treatment by delivering an integrated and personalised service. Wider adoption of such models through a collaborative and reiterative approach could help achieve HCV elimination.

ABSTRACTS
NASH patients with fibrosis stages 2 and 3 were randomized (1:1:1) to placebo (N=311), OCA 10 mg (N=312), or OCA 25 mg (N=308) once daily. Changes in FM (N=604), FM VCTE (N=604), and FAST (N=391) were analyzed using a mixed-effect repeated measures model (MRMM), with factors of treatment, baseline, visit, visit-by-treatment interaction, and stratification. Least square means and p-values were based on MMRM.

At baseline, no significant differences were observed in scores across treatment groups (figure 1). Patients with stage 3 fibrosis at baseline had higher scores than those with stage 2 fibrosis. OCA-treated patients experienced improvements in FM, FM VCTE, and FAST at Month 6 through Month 18. No improvements were observed with placebo (figure 1).

OCA treatment resulted in early and sustained improvements in non-invasive assessments of fibrosis in NASH. Improvements in FM and FM VCTE are consistent with OCA’s anti-fibrotic effect, while improvements in FAST are consistent with amelioration of NASH inflammation and fibrosis.

In an 18-month interim analysis of REGENERATE, obeticholic acid (OCA) improved steatohepatitis and fibrosis based on surrogate endpoints of liver histology in patients with non-alcoholic steatohepatitis (NASH). Liver biopsy has several limitations, and development of non-invasive tools for NASH diagnosis and monitoring is warranted. We evaluated the effects of OCA on multiparametric, MRI-derived, iron-corrected T1 (cT1) mapping, which is thought to correlate with hepatic fibroinflammatory disease and predict clinical outcomes.

Multiparametric MRI by LiverMultiScan (Perspectum Diagnostics, UK) was performed in a subset of REGENERATE NASH patients with fibrosis stage 2 or 3 (N=20) randomized 1:1:1 to placebo (n=7), OCA 10 mg (n=6), or OCA 25 mg (n=7). Changes in cT1 and liver fat content were evaluated following 18 months of treatment.

At baseline, mean (SD) cT1 was similar in the placebo, OCA 10-mg, and OCA 25-mg groups (856.7 [106.8] ms; 943.2 [116.11] ms; and 882.1 [94.75] ms, respectively). Following 18 months of treatment, a dose-dependent reduction in mean cT1 from baseline was observed (placebo: -1.4 ms; OCA 10 mg: -59.6 ms; OCA 25 mg: -91.7 ms). At baseline, mean liver fat content was 16.29% (placebo), 19.27% (OCA 10 mg), and 15.3% (OCA 25 mg). Modest reduction (-7.9%) in fat content occurred in the OCA 25-mg arm at 6 months and was generally sustained through 18 months (figure 1).

Treatment with OCA resulted in dose-dependent improvements in cT1 and liver fat content measured noninvasively by multiparametric MRI, which may be consistent with histologic improvements and serum-based non-invasive markers of steatohepatitis and fibrosis.

### Abstract P21 Figure 1
Fibroinflammatory disease and fat content by multiparametric MRI

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10.1136/gutjnl-2020-BASL.32