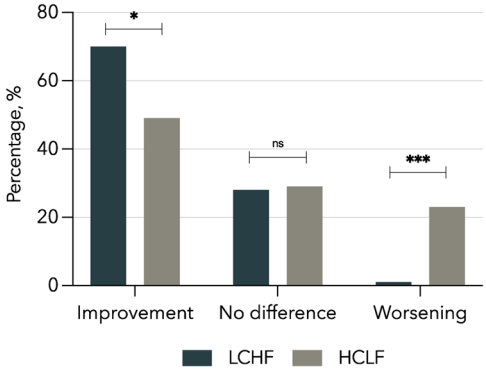

Figure: Change in NAS.

Conclusion: A six-month non-calorie-restricted LCHF diet improves NAS and HbA1c significantly more than a HCLF diet in people with T2DM.

Saturday 25 June

Late-Breaker

LB001

Semaglutide 2.4 mg once weekly improved liver and metabolic parameters, and was well tolerated, in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial

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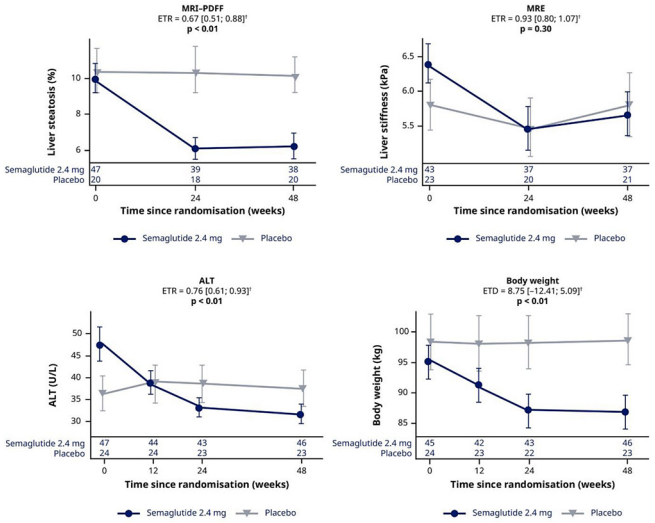
Background and aims: Patients with non-alcoholic steatohepatitis (NASH) and compensated cirrhosis (CC) are at high risk of liver-related and all-cause morbidity and mortality. In a previous placebo-controlled trial in patients with NASH without cirrhosis (NCT02970942), the glucagon-like peptide-1 receptor agonist semaglutide improved NASH resolution and associated metabolic parameters, and was well tolerated. We investigated the efficacy and safety of semaglutide in patients with NASH and CC.
Method: In a phase 2, randomised, placebo-controlled trial, adults with biopsy-confirmed NASH and CC, body mass index (BMI) ≥27 kg/m^2 and glycated haemoglobin (HbA_{1c}) ≤9.5% were randomised 2:1 to semaglutide 2.4 mg or placebo once weekly for 48 weeks. Histological parameters were assessed at baseline and week 48 by a single pathologist. The primary end point was the proportion of patients with ≥1 stage of liver fibrosis improvement without worsening of NASH after 48 weeks. Supportive secondary end points included NASH resolution, changes in: alanine- and aspartate-aminotransferase (ALT, AST); liver stiffness assessed by magnetic resonance elastography (MRE); liver fat content measured by magnetic resonance imaging proton density fat fraction (MRI-PDFF); cardiometabolic parameters; and exploratory biomarkers, and adverse events (AEs).
Results: Patients (N = 71) were mainly female (69%), with a mean age of 59.5 ± 8.0 years, BMI 34.9 ± 5.9 kg/m^2 and non-alcoholic fatty liver disease activity score 4.8 ± 1.0; 75% had type 2 diabetes. Baseline parameters were balanced between treatments. There was no difference between semaglutide and placebo for the primary end point (10.6% vs 29.2%; p = 0.09) or NASH resolution (34.0% vs 20.8%; p = 0.29). Compared with placebo, semaglutide reduced ALT (Figure), AST (estimated treatment ratio [ETR] 0.77; p < 0.01), MRI-PDFF but not MRE score (Figure), and pro-C3 levels (ETR 0.84; p = 0.03), and led to reductions in HbA_{1c} (estimated treatment difference −1.63; p < 0.01 for patients with diabetes) and body weight (Figure). Semaglutide also reduced triglycerides (ETR 0.83; p = 0.01) and very low-density lipoprotein cholesterol (ETR 0.83; p = 0.01). Similar proportions of semaglutide and placebo recipients reported AEs during the trial (89.4% vs 79.2%, of which 12.8% and 8.3%, respectively, were serious). Gastrointestinal AEs occurred in 76.6% of semaglutide recipients (vs 33.3% with placebo). Hepatic and renal function remained stable. There were no decompensating events or deaths.
Conclusion: Although the primary end point was not met, semaglutide 2.4 mg once weekly appeared safe, was well tolerated and improved cardiometabolic parameters and non-invasive markers of liver injury associated with fibrosis progression. Larger trials are needed to investigate whether semaglutide improves liver-related morbidity and mortality in patients with NASH and CC.



Number of observations per treatment group and visit is presented in the lower part of each plot. Error bars show the standard of the mean for observed values and 95% confidence limits for estimated means. †ETD/ETRs with 95% confidence intervals and two-sided p-values are from the same analysis. Missing data were inputed from the observed data in the placebo group using the same analysis of covariance model but without treatment as factor.

ETD = Estimated difference of absolute change from baseline between semaglutide and placebo. ETR = Estimated ratio of relative change from baseline between semaglutide and placebo.

ALT, alanine aminotransferase; ETD, estimated treatment difference; ETR, estimated treatment ratio; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction.