PARK CITY, UTAH - JANUARY 9-11, 2025

ABSTRACT BOOK

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

[4- DISTINGUISHED ABSTRACT]
ONCE-MONTHLY EFIMOSFERMIN ALFA (BOS-580) IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS WITH F2/F3 FIBROSIS: RESULTS FROM A 24 WEEK, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2 TRIAL

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Abstract Category: Therapeutic trials - MASH/liver fibrosis – Humans Clinical trial design

Background Information/Purpose – In a Phase 2a multiple dose/regimen study, efimosfermin alfa (BOS-580), an FGF21 analogue, significantly improved liver steatosis, markers of liver injury, and fibrosis in patients with phenotypic metabolic dysfunction-associated steatohepatitis (MASH). A Phase 2, randomized, double-blind, placebo-controlled study was conducted in patients with biopsy-confirmed MASH, F2/F3 fibrosis, and Nonalcoholic Fatty Liver Disease Activity Score (NAS) ≥4.(NCT04880031)

Methods – Patients (N=84) were randomized to receive once-monthly efimosfermin 300mg or placebo for 24 weeks. The primary endpoint was safety and tolerability. Exploratory endpoints included the proportion of patients achieving fibrosis improvement ≥1 stage without worsening of MASH, MASH resolution without worsening of fibrosis, ≥2 point improvement in NAS score, and a composite endpoint of fibrosis improvement ≥1 stage and MASH resolution.

Results – Patients (52.4% female; mean age 54 yrs; mean BMI 37.3 kg/m^2; mean HFF 20.6%; 43% F3 fibrosis; 57% type 2 diabetes) were administered efimosfermin 300mg (n=43), or placebo (n=41). In the biopsy analysis set, a significantly higher proportion of patients treated with efimosfermin 300mg (n=34) achieved improvement in fibrosis without worsening of MASH (45.2% v 20.6%, p=0.038), and resolution of MASH without worsening of fibrosis (67.7% v 29.4%, p=0.002) versus placebo (n=31). Additionally, a significantly higher proportion of patients achieved MASH improvement with ≥2 point improvement in NAS score without worsening of fibrosis (67.7% v 20.6%, p<0.001). The proportion of patients who achieved the composite endpoint of ≥1 stage fibrosis improvement and MASH resolution was 38.7% for efimosfermin 300mg versus 17.6% for placebo (p=0.066). In both groups, the most frequent treatment-related adverse events (AEs) were mild to moderate gastrointestinal events of nausea, diarrhea and vomiting. Overall, discontinuations were balanced with 2 efimosfermin patients who discontinued due to low-grade AEs. There was 1 treatment-related grade 3 serious AE.

Conclusions – Once-monthly efimosfermin significantly improved both regulatory key endpoints including MASH resolution and fibrosis improvement at 24 weeks in patients with F2/F3 fibrosis due to MASH. In this study, efimosfermin was generally well-tolerated with a low rate of discontinuation due to AEs. These data support further development of once-monthly efimosfermin for the treatment of MASH-related fibrosis.

[7- DISTINGUISHED ABSTRACT]
Reasons for discontinuation of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) among patients with MASH: An analysis of real-world clinical notes

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***B*ackground Information/Purpose –**Many patients with MASH are taking glucagon-like peptide-1 receptor agonists (GLP-1 RAs) to manage comorbid diagnoses of type 2 diabetes and obesity, and these drugs are currently under investigation for treatment of MASH. The efficacy of these medications in achieving lasting metabolic benefits relies on sustained treatment. Although recent literature shows that discontinuation can occur within the first year of treatment, data are limited regarding the reasons for discontinuation. The aim of this exploratory, descriptive analysis of provider notes was to characterize documented reasons for discontinuation of GLP-1 RAs.

Methods – Using electronic health records (EHR) from the Veradigm Network EHR, we identified patients with ≥1 GLP-1 RA prescription, a documented end date between June 1, 2012, and July 1, 2024, and a clinical note on the end date of treatment. We required that patients were ≥18 years old and had a diagnosis of MASH. We excluded patients with cirrhosis, type 1 diabetes, or gestational diabetes at any time. We identified a subset of notes with the name of a GLP-1 RA and one of several stop terms (stop, stopped, discontinued, discontinue, discontinuation, d/c, gap, quit), and the free text was examined for common reasons for discontinuation. A subanalysis was performed on patients stratified by time to discontinuation (≤6 months or >6 months) by looking back through the EHR to determine the first documented prescription.

Results – We identified 266 qualifying patients with MASH, whose mean age was 55.0 years old. Overall, 66.8% were female, 79.3% had a prior diagnosis of T2D, and 84.2% had prior evidence of obesity. Most patients indexed on semaglutide (47.9%) or dulaglutide (24.9%). We pulled relevant portions from 363 clinical notes and found that side effects/adverse events were the most commonly documented reason for stopping therapy (n=129 [35.5%]) and were reported as the reason for discontinuation among 39.1% (59 of 151) of those who discontinued within the first 6 months and of those who discontinued after 6 months 33.0% (70 of 212). Other common reasons included switched medications (n=55 [15.2%]) and cost/insurance barriers (n=32 [8.8%]).

Conclusions – In this exploratory, descriptive analysis of GLP-1 discontinuation in patients with MASH, side effects or adverse events were the most commonly documented reason for discontinuation.

[17- DISTINGUISHED ABSTRACT] WEIGHT LOSS-RELATED CHANGES IN MRI-DERIVED MEASURES OF BODY COMPOSITION AND LIVER HEALTH: A LARGE-SCALE ANALYSIS FROM THE UK BIOBANK

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Abstract Category: Pathogenesis, Translational Science, NAFLD/MASH, Liver Fibrosis, Humans

Background Information/Purpose –With the increased global prevalence of obesity and recent advancements in weight-loss therapies, tracking the distribution of fat after weight loss and its impact on liver health could aid in optimizing treatment plans and identifying new drug targets. The aim of this study was to assess weight loss-related changes in adipose tissue, skeletal muscle, and the associated changes in liver fibro-inflammation and fat content using MRI, in a large-scale cohort from the UK Biobank

Methods –Participants (N=3,919) from the UK Biobank with whole-body Dixon MRI scans from two visits, spaced 1-3 years apart (mean 2.6 years), were included. MRI data were processed automatically to derive volumetric visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and skeletal muscle (SM) in the abdominal region. Liver fat content (LFC from proton density fat fraction) and liver fibro-inflammation (cT1) were assessed using LiverMultiScan. Participants were categorized into two groups based on relative weight change between visits: ≥5% weight loss and <5% weight loss (causes of weight loss were not investigated). Within-group comparisons were conducted using the paired Wilcoxon signed-rank test, while between-group comparisons were assessed with the Wilcoxon rank-sum test.

Results – In the ≥5% weight loss group (N=415, mean age 64 years, male 47%, BMI 27 kg/m^2, baseline VAT 3.9 litres (L), SAT 7L, SM 5.4L, LFC 3.6%, cT1 703ms), significant reductions from baseline were observed: LFC -25%, VAT of -27%, SAT of -21%, and SM of -3.4% (all p<.001). Liver cT1 decreased by 1.2% (10ms), which was not clinically significant. In the <5% weight loss group (N=3,294, mean age 63 years, male 51%, BMI 26 kg/m^2, baseline VAT 3.2L, SAT 6L, SM 5.5L, LFC 3%, SM 5.5L, cT1 689ms), no significant reductions were observed in any of the body composition or liver metrics. Between-group comparisons showed significant differences across all metrics (p<.001).

Conclusions – Individuals who lost ≥5% weight demonstrated substantial reductions between imaging visits in liver fat, VAT, SAT, and skeletal muscle volume, and compared to the <5% weight loss group. Reductions in liver fat were not accompanied by parallel improvements in metrics of liver fibro-inflammation. While ≥5% weight loss significantly improves MRI adiposity-related measures, targeted therapeutic strategies may be necessary to prevent muscle loss and improve liver fibro-inflammation.

[18- DISTINGUISHED ABSTRACT] CHANGE IN CT1 FOLLOWING INTERVENTIONS IN MASLD: A SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS

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Abstract Category: Clinical Trial Design

Background Information/Purpose –Liver cT1, measured with multiparametric MRI, offers an alternative to liver biopsy to monitor treatment response. However, a systematic evaluation of the change in liver disease activity based on cT1 following intervention in adults with metabolic associated steatotic liver disease (MASLD) has not yet been performed.

Methods – We searched the Cochrane Library, PubMed Central, and MEDLINE from 2014 to September 2024 for studies that incorporated cT1 and examined responses following intervention in adults with MASLD and associated terms. Two authors independently screened records, assessed risk of bias and extracted data. Meta-analyses were performed on study-specific changes in cT1 values to yield the mean change between baseline and follow-up for each cohort on treatment and placebo, as well as the cT1 response rate.

Results – A total of 22 records comprising a total of 1325 individuals from 18 studies met the eligibility criteria for inclusion in the systematic review: one phase 3 trial (n = 20), twelve phase 2 trials (n = 1133), two randomized, double-blind, prospective studies (n = 115) and three prospective lifestyle and bariatric surgery studies (n = 57). All individuals were deemed to meet the clinical diagnostic criteria for MASLD and, in 16 studies, for MASH (metabolic-associated steatohepatitis). The meta-analysis included 16 studies comprising of 1145 individuals and showed that cT1 had a mean change of -56ms [95% CI: -64ms, -48ms]. In subgroup analyses by treatment type, FGF analogs (aldafermin; pegozafermin), GLP-1 receptor agonists (pemvidutide; tirzepatide) and FXR agonists (vonafexor; ocaliva; TERN-101) cT1 had a mean change of -77ms [95% CI: -94ms, -60ms], -71ms [95% CI: -85ms, -56ms] and -59ms [95% CI: -80ms, -38ms], respectively. In contrast, the placebo responses showed a mean change in cT1 of -4ms [95% CI: -17ms, 9ms].

Conclusions – Evidence to-date supports a significant treatment-induced reduction in cT1 as compared to minimal changes in the placebo group. Our findings could inform current and future study designs for investigational therapies for liver disease (including MASLD) and support treatment response monitoring in individuals with MASLD in clinical trials and clinical practice.

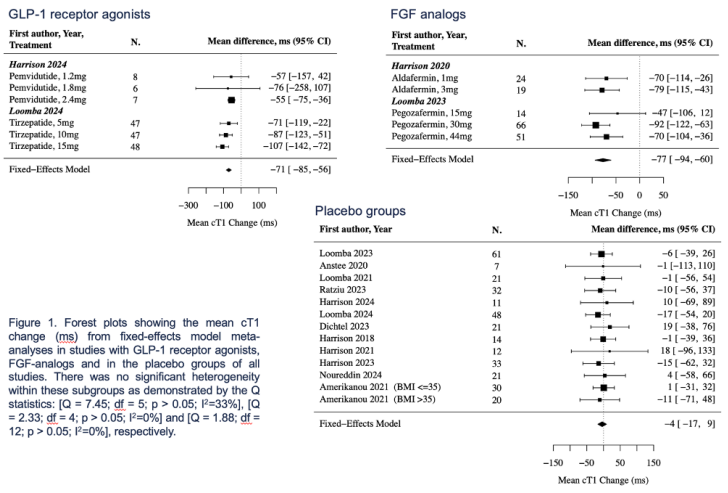

Figure 1. Forest plots showing the mean cT1 change (ms) from fixed-effects model meta-analyses in studies with GLP-1 receptor agonists, FGF-analogs and in the placebo groups of all studies. There was no significant heterogeneity within these subgroups as demonstrated by the Q statistics: [Q = 7.45; df = 5; p > 0.05; I^2=33%], [Q = 2.33; df = 4; p > 0.05; I^2=0%] and [Q = 1.88; df = 12; p > 0.05; I^2=0%], respectively.

[21- DISTINGUISHED ABSTRACT] RESMETIROM THERAPY OF MASH-ASSOCIATED CHILD PUGH A CIRRHOSIS REDUCES ESTIMATED RISK FOR CLINICAL OUTCOME BASED ON HEPQUANT RISK ACE MODEL

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Abstract Category: Diagnostic procedures for MASH/Liver fibrosis

Background Information/Purpose – Resmetirom has been FDA-approved for use in F2/F3 MASH and is under study for use in cirrhosis. The HepQuant DuO test quantifies liver function and physiology from the clearance of orally administered isotopes of cholate. In this study, MAESTRO-NAFLD-1 (NCT04197479), an open label, single arm study of resmetirom in Child Pugh A cirrhosis, we used serial monitoring with DuO to quantify changes in liver function and portal-systemic shunting.

Methods –The Disease Severity Index (DSI) from DuO was measured in 23 subjects with compensated MASH cirrhosis (eligibility required at least 3 metabolic risk factors, and MASH cirrhosis diagnosed on liver biopsy or according to accepted criteria) at baseline and at 28 (W28) or 48 weeks (W48). For each test, oral deuterium-labelled cholic acid (d4-CA) was administered, blood was sampled at 20 and 60 minutes, serum d4-CA concentrations were measured by LC-MS/MS, and test parameters including DSI were calculated. A Cox proportional hazards regression model (manuscript in progress) linking DSI to clinical outcome, Risk for Adverse Clinical Event (RISK ACE), was developed from 220 HCV subjects with 52 clinical decompensating events in the HALT-C trial. RISK ACE was evaluated for each of these 23 subjects in MAESTRO-NAFLD-1.

Results – At W48 of resmetirom, 39% of subjects showed improvement from baseline (DSI reduction >2; Chi-square, p=0.046), 44% had stable hepatic function (ΔDSI within ±2), and 17% showed worsening (DSI increase >2). The 1-year risk of adverse clinical events decreased at W48 with resmetirom treatment, with a significant reduction in average risk from baseline (−3.97%, p=0.041). Subjects with greater hepatic impairment by DSI at baseline showed greater reduction in RISK ACE at W28 and W48. At W48, the stabilization or change in DSI from baseline to W48 lowered the estimation of an adverse clinical event within 1 year by 0.14% for low risk (baseline DSI <18.3, p=0.372), 1.7% for moderate risk (baseline DSI 18.3–24, p<0.0001), and 8.1% for high risk (baseline DSI ≥24, p<0.047).

Conclusion: This study demonstrated that 48 weeks of resmetirom in MASH-associated Child Pugh A cirrhosis is associated with estimated reduction in adverse clinical events as assessed by HepQuant's RISK ACE Model. These results show potential for DuO and RISK ACE to provide a sensitive and interpretable metric of risk in monitoring patients during treatment trials.

Disclosures: MPM is a paid consultant for HepQuant, LLC. GTE is an employee and equity member of HepQuant, LLC. RT is an employee of Madrigal Pharmaceuticals. MPM and GTE have provisional patents pending. This abstract has been presented as a poster at AASLD 2024.

[40- DISTINGUISHED ABSTRACT] PHASE 3 ESSENCE TRIAL: SEMAGLUTIDE IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH)

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Abstract Category: Diagnostic procedures for MASH/Liver fibrosis

Background Information/Purpose – Semaglutide, a glucagon-like peptide-1 receptor agonist, is a candidate for the treatment of metabolic dysfunction-associated steatohepatitis (MASH). Semaglutide is being investigated for its potential to treat MASH in the phase 3 ESSENCE trial.

Methods –ESSENCE, an ongoing multi-center, phase 3 randomized, double-blind, placebo-controlled outcome trial involving 1200 participants with biopsy-defined MASH and fibrosis stage F2/F3, randomized participants 2:1 to once-weekly subcutaneous semaglutide 2.4 mg or placebo for 240 weeks. A planned interim analysis at week 72 of the first 800 participants evaluated the trial's primary endpoints: resolution of steatohepatitis with no worsening of liver fibrosis, and improvement in liver fibrosis with no worsening of steatohepatitis.

Results – Among the 800 participants (semaglutide [n=534; 169 F2, 365 F3] or placebo [n=266; 81 F2, 185 F3]), mean (standard deviation [SD]) age was 56.0 (11.6) years and body mass index was 34.6 (7.2) kg/m^2. Most participants were White (67.5%), female (57.1%) and 55.9% had type 2 diabetes at baseline; 250 (31.3%) participants had F2 and 550 (68.8%) had F3. Resolution of steatohepatitis with no worsening of fibrosis was achieved by 62.9% of participants in the semaglutide group vs 34.1% receiving placebo, with an estimated difference in responder proportions (EDP) of 28.9% (95% CI, 21.3 to 36.5; P<0.0001). Improvement in liver fibrosis with no worsening of steatohepatitis was achieved by 37.0% (semaglutide) and 22.5% (placebo) (EDP, 14.4%; 95% CI, 7.5 to 21.4; P<0.0001), while 32.8% (semaglutide) and 16.2% (placebo) achieved combined resolution of steatohepatitis with improvement in liver fibrosis (EDP, 16.6%; 95% CI, 10.2 to 22.9; P<0.0001). There were improvements in liver enzymes and non-invasive fibrosis markers. As expected, improvements in body weight and cardiometabolic parameters were also observed. The incidence of serious adverse events in the safety analysis set was similar in both arms.

Conclusion: In participants with MASH and moderate to advanced liver fibrosis, semaglutide 2.4 mg once-weekly demonstrated superiority vs placebo for improvement of histological activity and fibrosis markers, thus meeting both primary endpoints after 72 weeks of treatment. In addition, semaglutide improved MASH injury and fibrosis biomarkers and cardiometabolic features.
(Funded by Novo Nordisk A/S; ESSENCE ClinicalTrials.gov number, NCT04822181)..

[14]

LIQUID BIOPSY USING WHOLE GENOME METHYLATION CELL-FREE DNA SIGNATURE FOR NON-INVASIVE DIAGNOSIS OF AT-RISK MASH

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Abstract Category: Diagnostic Procedures - MASH/Liver Fibrosis

Background Information/Purpose – The advent of the first treatment for MASH highlights the need for a single rule-in non-invasive blood test (NIT) to identify treatment candidates at scale. The aim of this cross-sectional analysis is to examine the diagnostic accuracy of a whole methylome-sequencing cell-free DNA panel for the diagnosis of at-risk MASH among patients with biopsy-proven MASLD.

Methods –We analysed 276 plasma samples from Duke University Biobank, using deep whole methylome sequencing to explore the methylation patterns for hundreds of millions of cell-free DNA molecules per sample.
We used a random 2-to-1 split of samples for training and validation sets. A novel transformer model, a neural network that learns the context and interactions between millions of unique molecules, was specifically trained to detect at-risk MASH (NAS≥4 and F2+). AUC and positive likelihood ratio (PLR) were compared to FIB4 and other major tests in the literature. A methylome-wide association to study relevant genes and pathways was also performed.

Results-The study cohort included 217 participants with biopsy-proven MASLD and 59 control subjects without histologic MASLD with the following breakdown for 217 subjects with MASLD: F0: 59, F1: 53, F2: 31, F3: 47, F4: 27, with 123 having NAS ≥ 4. Age and BMI of controls and MASLD subjects were similar. The diagnostic accuracy of the whole-genome methylation signature panel for the diagnosis of F2+ with NAS≥4 in the validation set demonstrated an AUC of 0.86 [0.77-0.94] and PLR of 10.09 [8.74-13.4], which was both clinically and statistically significant. The performance was statistically significantly better than FIB4 which had AUC 0.69 [0.58-0.79] and PLR 3.25 [2.71-4.06] on this dataset. This performance far surpasses that of state-of-the-art NITs reported in the literature. Further, the methylome-wide association shows differences in genes known to regulate pathways that drive MASH progression.

Conclusions- Whole methylome sequencing in conjunction with advanced AI provided a highly accurate tool for the non-invasive diagnosis of at-risk MASH. The biological plausibility of the model was further confirmed by loci, genes and pathways that were different between groups which not only provides confidence in the method but may also shed light on the biological underpinning of the disease. The presented model provides a superior PLR and has the potential as a reliable single-test approach to rule-in at-risk MASH and guide treatment.

[15]

ISERUM PROTEOMICS TO UNRAVEL THE ROLE OF INSULIN RESISTANCE IN RARE AND COMMON STEATOTIC LIVER DISEASES

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Abstract Category: Pathogenesis, translational science, NAFLD/MASH, liver fibrosis, humans

Background Information/Purpose – Metabolic dysfunction-associated steatotic liver disease (MASLD) is linked to obesity-associated metabolic syndrome and insulin resistance (IR). In obesity-associated IR and in lipodystrophy (LD), a rare condition of missing adipose tissue, hyperinsulinemia stimulates excess hepatic lipogenesis, leading to steatotic liver disease (SLD). In contrast, in insulin receptor pathogenic variants (INSR), despite hyperinsulinemia and marked IR, hepatic lipogenesis and steatosis are not promoted. We hypothesized that MASLD, LD, and INSR share commonalities and differences in serum proteome, explaining pathophysiology of SLD.

Methods –A cross-sectional single-center study (NCT02520609, NCT00001987) of fasting serum proteome using SomaScan assay v4.1 in 30 people with LD, 29 with INSR, 16 with obesity-associated MASLD. GO enrichment was used for pathway analyses. Key targets were assessed in hepatic transcriptome of people with MASLD (n=19) and using in-vitro studies in HepG2 cells.

Results: Of 6,412 unique proteins measured, 567 differed between at least two groups. The three groups were separated by the proteome; INSR was clearly distinct from LD and MASLD, which were more similar, mainly driven by proteins involved in metabolic processes and previously associated with liver injury and fibrosis. As anticipated, INSR and MASLD had higher levels of leptin and adiponectin compared to LD. Compared to INSR, both MASLD and LD demonstrated higher serum levels of alcohol dehydrogenases 1A and 4, glutathione-S-transferases alpha 1 and 2, aldolase B and fructose-1,6-biphosphotase, as well as TREM2. Several proteins were uniquely elevated in INSR and LD compared to MASLD, particularly Factor IX (F9) and liver-expressed antimicrobial peptide 2 (LEAP2). F9 and LEAP2 were highly correlated in serum and hepatic transcriptome; their expression in-vitro was unaffected by leptin, insulin, or glucose treatment.

Conclusions: This first comparative study of proteomics in disorders with IR identified shared and unique pathways. MASLD and LD share many proteomic features, suggesting similar drivers of liver disease progression. However, key liver-derived proteins differ between MASLD, INSR and LD, due to unique features of each disorder. We demonstrate the utility of proteomics and the study of rare disorders in interrogating the pathogenesis of common disorders like MASLD.

[16]
FIRST-IN-HUMAN PHASE 1 STUDY OF THE SAFETY AND PHARMACODYNAMIC EFFECTS OF OA-235I, A PAR2 PEPDUCIN, IN ADULTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) AND STEATOHEPATITIS (MASH)

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Abstract Category: Therapeutic Trials - MASH/Liver Fibrosis – Humans

Background Information/Purpose –MASH, the progressive form of MASLD, is characterized by steatosis and necroinflammation with or without hepatic fibrosis. Resmetirom, a thyroid hormone-derived metabolic drug, recently received conditional FDA approval based on its safety and efficacy on surrogate endpoints of MASH resolution and fibrosis regression. However, there remains an unmet need for more effective therapies to mitigate MASH fibrosis and its associated metabolic comorbidities which contribute to disease progression and poor clinical outcomes. Cell surface protease-activated receptor 2 (PAR2) drives several critical pathways of MASH progression, fibrosis and metabolism. Liver PAR2 expression increases with diabetes and hepatic fibrosis in patients with MASH and in preclinical models of MASH, diabetes and obesity.

Methods – In a Phase 1a/1b randomized, placebo-controlled study, OA-235i, a Pepducin™ inhibitor which targets the cytoplasmic surface of the PAR2 receptor, was evaluated for safety, pharmacokinetics and target engagement in adults with MASH/MAFLD. 15 subjects received OA-235i (sc) in 5 ascending single-dose cohorts (4-40 mg) and 9 subjects were randomized to OA-235i or placebo (3:1) in a 7-day multi-dose (20-40 mg) study.

Results – OA-235i was well tolerated with no hemodynamic, laboratory adverse events, SAEs, nor GI side-effects observed following daily single or multi-doses. There was a dose-dependence of both mean Cmax and drug exposure, peaking at the 30-40 mg doses. OA-235i rapidly appeared in blood at the 30 min time point, reached Cmax at 4-6 h, with high drug levels maintained for at least 24 h with no drug detected in urine. Consistent with pre-clinical studies, improvements in blood glycemic indices, and ketones indicating stimulation of fatty acid beta-oxidation, was observed at both day 1 and after 7 days of multi-dosing. OA-235i caused a 25% reduction in plasma triglycerides and 13-18% increases in HDL-cholesterol levels from days 1-14.

Conclusions – OA-235i, a PAR2 inhibitor, is safe and well-tolerated. Early efficacy signals on metabolic parameters at up to 7 days following the last dose justify further investigation of PAR2 as a therapeutic target for treatment of MASH.

[28]
GM-60106: A HTR2A ANTAGONIST FOR THE TREATMENT OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH)

Hail Kim

Abstract Category: Therapeutic Trials - MASH/Liver Fibrosis – Humans

Background Information/Purpose – Metabolic dysfunction-associated steatotic liver disease (MASLD), including metabolic dysfunction-associated steatohepatitis (MASH), is a growing global health concern, with current treatments showing limited efficacy. This highlights the urgent need for innovative therapeutic strategies. This study explores the mode of action of GM-60106, a peripheral serotonin receptor 2A (5HT2A) antagonist, and evaluates its safety and tolerability in healthy adults and individuals with elevated MASLD/MASH markers in a Phase 1 trial (NCT05517564).

Methods – Using both genetic and pharmacological interventions, we evaluated 5HT2A inhibition on MASLD/MASH and liver fibrosis in multiple murine models, including STZ+HFD, CCL4-induced, and bile duct ligation models, to investigate 5HT2A as a potential therapeutic target.

The Phase 1 trial of GM-60106 is a randomized, double-blind, placebo-controlled study to evaluate single and multiple ascending doses in healthy adults and individuals with elevated MASLD/MASH markers. The trial comprises three parts:

- Part A (single ascending dose, SAD): 64 participants across 8 cohorts.
- Part B (multiple ascending dose, MAD): 24 participants across 3 cohorts receiving once-daily doses for 14 days.
- Part C (MAD): 8 participants with MASLD/MASH markers receiving once-daily doses for 28 days.

Results – 5HT2A expression increased in hepatocytes after high fat diet and in hepatic stellate cells during their activation. 5HT2A knockout in hepatocytes significantly reduced lipid accumulation, inflammation, hepatocyte ballooning and hepatic fibrosis. In addition, 5HT2A knockout in hepatic stellate cells markedly decreased fibrosis across various murine models. Furthermore, GM-60106 showed better efficacy in reducing MASLD/MASH progression and hepatic fibrosis compared to Resmetirom.
The clinical results from the JDB-106001 study confirm that GM-60106 is both safe and well-tolerated, supporting its potential as a promising therapeutic candidate.

Conclusions – In conclusion, these findings highlight the therapeutic potential of targeting 5HT2A for the treatment of MASLD/MASH. GM-60106 showed significant efficacy in preclinical models by reducing lipid accumulation, inflammation, and fibrosis, outperforming current treatments like Resmetirom. The Phase 1 clinical study further validated GM-60106's safety and tolerability, positioning it as a promising candidate for long-term treatment strategies to address the needs of patients with MASLD/MASH.

Acknowledgement:
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[42]
BELAPECTIN ADMINISTERED AT 2MG/KG/LBW FOR 18 MONTHS REDUCED THE INCIDENCE OF VARICES DEVELOPMENT IN PATIENTS WITH MASH CIRRHOSIS AND PORTAL HYPERTENSION: TOP LINE RESULTS FROM THE NAVIGATE TRIAL

Naim Alkhouri, Raj Vuppalanchi, Khurram Jamil, Seth Zuckerman, Stephen A Harrison, Naga Chalasani

Abstract Category: Therapeutic Trials - MASH/Liver Fibrosis – Humans

Background Information/Purpose – Therapeutic options for MASH cirrhosis are quite limited. In a previous study, we have shown that belapectin, a novel galectin-3 inhibitor, reduced HVPG and the development of varices in a subgroup of patients of MASH cirrhosis with no varices at baseline (Chalasani et al. Gastroenterology 2020; 158: 1334-1345).To follow-up on this therapeutic signal, the NAVIGATE trial was conducted to test the efficacy and safety of two doses of belapectin in patients with MASH cirrhosis without varices at baseline. Here, we present topline results from the NAVIGATE trial.

Methods – NAVIGATE is a global Phase 2b/3 clinical trial investigating belapectin, a novel galectin-3 inhibitor, in patients with MASH cirrhosis and portal hypertension but no varices by endoscopy. The study evaluated two dosing regimens of belapectin administered intravenously over 18 months, compared to placebo. Subject were stratified based on status of Type 2 DM, into Belapectin 2 or 4 mg/LBW or placebo. Enrollment criteria included non-invasive markers of portal hypertension in MASH cirrhosis patients. Baseline and end-of-treatment EGDs were performed to assess the incidence of varices; only subjects without varices were enrolled in the trial. The analysis included both an intent-to-treat (ITT) population and a per-protocol population to evaluate the effectiveness of therapy. The primary endpoint was the incidence of varices, defined as a composite endpoint, with a pre-specified per protocol analysis focusing on the reduction of varices development in all subjects who underwent EGD at baseline and at the end of the 18-month treatment period. EGDs were read centrally in a blinded fashion by at least two reviewers.

Results – 357 subjects were randomized across three cohorts, two subjects with varices at baseline were excluded from ITT population. Each cohort had 119 subjects randomized. 66 subjects didn't complete the 18-month treatment period. Baseline characteristics were comparable across three cohorts, included mean age of 60 years, 64.8% females, 90.7% white and 29.9% Hispanic, platelet count of 131.4k/ ul, Liver Stiffness of 24.8 kPa. In the ITT population, the incidence of varices was 17.8% in the placebo group compared to 10.1% in the 2 mg belapectin cohort, representing a 43.2% reduction (p=0.13.). In the per-protocol population, the incidence was 22.1% in the placebo group versus 11.3% in the 2 mg belapectin cohort, a ~ 50% reduction in the development of varices (p = 0.03).Belapectin administered at 4 mg/kg/LBW did not have significant effect on the incidence of varices wither in the ITT (p=0.5) or per-protocol (p=0.12) populations. Both doses of belapectin were well tolerated and no safety signals were identified. Notably, these findings for the 2 mg cohort reproduce the results observed in our previous phase2 study.

Conclusions – Belapectin, a novel galectin-3 inhibitor, administered at 2 mg/kg/LBW demonstrated a favorable reduction in the development of varices in the ITT population and a statistically significant reduction in the per-protocol population at 18 months. Data from the 36-month follow-up period are awaited, with the potential to provide further insights into longer-term efficacy. These encouraging results support the continued investigation of belapectin in a Phase 3 clinical trial to further evaluate its role in managing MASH cirrhosis with portal hypertension.

[1]
THE PAN-PPAR AGONIST LANIFIBRANOR IMPROVES LIVER INFLAMMATION, BALLOONING, AND FIBROSIS IN A DIET-INDUCED OBESE MASH HAMSTER MODEL OF BINGE DRINKING.

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Abstract Category: Experimental/basic science, NAFLD/MASH, non-humans

Background Information/Purpose – We aimed to setup an animal model to evaluate the efficacy of drugs targeting MASH in a context of moderate to heavy alcohol use, which may aggravate liver lesions in patients with MASH. Because mouse and rat are not convenient models to study the effects of alcohol, our objective was to validate a diet-induced obese MASH hamster model of binge drinking, as this species spontaneously shows a high preference for alcohol. Therefore, we tested the effects of lanifibranor (LANI), a pan-PPAR agonist currently evaluated in phase III trial for the treatment of MASH.

Methods – Diet-induced obese MASH hamsters were gavaged with saline (control) or with alcohol binge drinking (40% alcohol at 10mL/kg p.o., 3 times per week), and were simultaneously treated with vehicle or LANI 30mg/kg p.o. QD for 5 weeks.

Results – Compared to control, binge drinking in obese MASH hamsters led to higher plasma triglycerides levels, hepatic inflammation and ballooning scores and greater liver fibrosis, as measured with % Sirius Red labelling (all $p<0.05$). Binge drinking significantly raised the expression of genes involved in lipogenesis (ACC and SCD1), inflammation (IL-1b, IL-6, and MCP-1), cell death (caspase 3) and fibrosis (a-SMA, Col1a1 and TIMP1). Compared to hamsters treated with both binge drinking and vehicle, LANI significantly lowered total cholesterol, LDL-cholesterol, and triglycerides plasma levels. Liver triglycerides content, hepatic inflammation and ballooning scores, as well as liver fibrosis were all reduced with LANI (all $p<0.05$ vs. vehicle).

Conclusions – LANI significantly improved dyslipidemia and liver lesions in our obese MASH hamster model of binge drinking, which should help evaluating drugs targeting MASH in a context of moderate to heavy alcohol use.

[3]

LONG-TERM COST-EFFECTIVENESS OF FIB-4 AND ENHANCED LIVER FIBROSIS (ELF) TESTING STRATEGIES FOR INITIAL EVALUATION OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IN A VETERAN POPULATION.

Artem T. Boltyenkov, PhD

Abstract Category: Diagnostic Procedures - MASH/Liver Fibrosis

Background Information/Purpose – We assessed the long-term cohort-based cost-effectiveness of FIB-4 and ELF testing strategies of adult patients with obesity and/or type 2 diabetes mellitus (T2DM), a major risk factor of MASLD, in the primary care setting at the Veteran Affairs Palo Alto Healthcare System (VAPAHCS) in Palo Alto, CA.

Methods – Patients with obesity and/or T2DM identified using electronic medical records at VAPAHCS underwent fibrosis 4 (FIB-4) and ELF testing. A cost-effectiveness analysis (CEA) was conducted to compare six testing strategies in this population: FIB-4 alone at 1.3 cut-off, ELF alone with 9.0 and 9.8 cut-offs, and FIB-4 followed by ELF (FIB-4/ELF) with 7.7, 9.0 and 9.8 cut-offs at a willingness-to-pay threshold of $100,000/QALY gained in terms of long-term health care costs and lifetime quality-adjusted life years (QALYs). We developed a microsimulation model to simulate disease-related events among a cohort of 254 VA patients based on their individual test scores, age, and BMI over their lifetime with annual cycles. Parameter uncertainty was captured from 1,000 parameter samples. Costs were adjusted to 2024 U.S. dollars to evaluate the long-term effect of each testing strategy from a healthcare perspective.

Results – Patients (n=254) were enrolled with a mean age 65.3+/-9.3 years, and a mean body mass index (BMI) of 31.7+/-6. Of these patients, 87.4% were male, 78.3% non-Hispanic, and 96.5% had T2DM. The FIB-4/ELF with the 9.8 cut-off strategy was cost-effective in 50.50% of the simulations, while the ELF alone strategy with the 9.0 cut-off was cost-effective in 0.4% of the simulations. A single test FIB-4 strategy, the current standard-of-care at VAPAHCS, was cost-effective in 21.90% of the simulations. Total costs per person were lowest for the FIB-4/ELF with the 9.8 cut-off ($28,474) and highest for the ELF alone strategy with the 9.0 cut-off ($35,008). The FIB-4 alone strategy had a cost of $29,623. Lifetime QALYs were lowest for ELF alone strategy with 9.0 cut-off (13.52) and highest for FIB-4/ELF with the 9.8 cut-off strategy (14.24). FIB-4 alone strategy has a lifetime QALY of 14.09. The CEA revealed that the FIB-4/ELF with 9.8 cut-off strategy dominated all other strategies consisting of FIB-4 and/or ELF.

Conclusions – A FIB-4 followed by ELF strategy with the 9.8 cut-off can be a cost-effective gatekeeping tool for veteran patients with obesity and/or T2DM in the primary care setting at risk for MASLD in the United States.

[6]

ALG-055009, A NOVEL THYROID HORMONE RECEPTOR BETA (THR-B) AGONIST, WAS WELL-TOLERATED WITH SIGNIFICANT REDUCTIONS IN LIVER FAT AT WEEK 12 IN NON-CIRRHOTIC MASH PATIENTS IN THE RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 2A HERALD STUDY

Rohit Loomba[1], Dimple Desai[2], Daniel Santillano[3], Kathryn Jean Lucas[4], Naim Alkhouri[5], Guy Neff[6], Antonio Bianco[7], Eveline Bruinstroop[8], Stanley Wang[9], Kha Le[9], Megan Fitzgerald[9], Min Wu[9], Ifong Kan-Eng[9], Genevieve Harrington[9], Melissa San Nicolas[9], Chris Burnett[9], Jen Rito[9], Doug Clark[9], Naqvi Mohammed[9], Meenakshi Venkatraman[9], Tse-I Lin[9], Sushmita Chanda[9], Hardean E. Achneck[9], Lawrence Blatt[9], Christos S. Mantzoros[10]

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Abstract Category: Therapeutic Trials - MASH/Liver Fibrosis – Humans

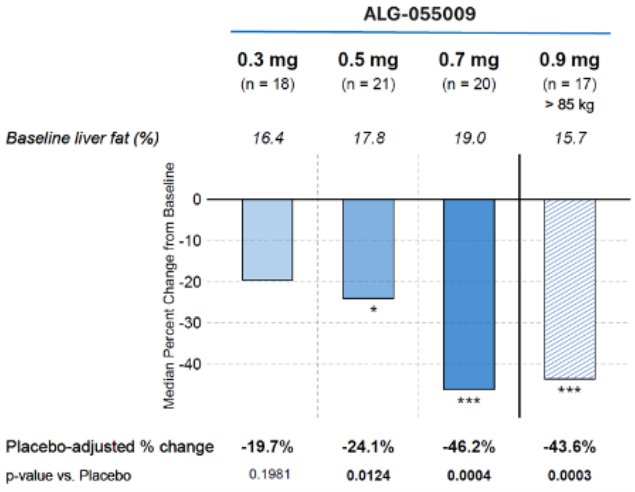
Background Information/Purpose – ALG-055009 is a novel next generation THR-β agonist with β selectivity and in vitro potency exceeding first generation drugs. Ph2a HERALD was a randomized, double-blind, placebo-controlled study evaluating the efficacy, safety, pharmacokinetics and pharmacodynamics of ALG-055009 in adults with presumed MASH and F1-F3 fibrosis; final analysis results are reported here.

Methods – 102 subjects (~20/arm) were randomized to receive 0.3, 0.5, 0.7 or 0.9 mg ALG-055009 or placebo orally once daily for 12 weeks. Only subjects with body weight >85 kg were enrolled in the 0.9 mg arm, with no weight restrictions for other arms. The primary endpoint was relative change from baseline in liver fat by MRI-PDFF at Week 12. Lipid/lipoproteins levels, sex hormone binding globulin (SHBG), MASH/fibrosis biomarkers and safety/tolerability were assessed.

Results – Baseline characteristics were generally similar across arms: 62% female, mean age 50 yrs, mean BMI 39 kg/m^2, 46% Type 2 diabetes. ALG-055009 dose groups met the primary endpoint, with statistically significant placebo-adjusted median relative reductions in liver fat of up to 46.2% at Week 12 with a dose response between 0.3-0.7 mg (Figure). Among 18 subjects with baseline stable GLP-1 agonist use, 11/14 treated with ALG-055009 had liver fat decreases and 4/4 treated with placebo had liver fat increases. Up to 70% of subjects achieved ≥30% relative reduction in liver fat compared to baseline. Significant reductions in LDL-C, lipoprotein(a) and apolipoprotein B, regardless of baseline GLP-1 agonist use, and dose-dependent SHBG increases were observed. The majority of treatment emergent adverse events (TEAEs) were mild to moderate, with no SAEs in subjects receiving ALG-055009 and one discontinuation due to worsening insomnia in a subject with pre-existing insomnia (Table). No clinically meaningful findings in laboratory tests, ECGs, vital signs, physical exams or clinical evidence of hypo/hyperthyroidism were observed. Incidence of gastrointestinal (GI)-related TEAEs, including diarrhea, were similar in ALG-055009 dose groups versus placebo.

Conclusions – 12 weeks of once daily ALG-055009 treatment in MASH subjects met the primary endpoint, demonstrating significant reductions in liver fat and was well-tolerated, with rates of GI-related TEAEs similar to placebo. Additional liver fat reduction was observed among subjects with stable GLP-1 agonist use.This supports evaluation of longer durations of ALG-055009 and its effects on liver histology.

Figure: Placebo-adjusted Median Relative Change in Liver Fat at Week 12



Note: Data from MRI-PDFF analysis dataset, defined as all randomized subjects who have MRI-PDFF measurements available at both baseline and Week 12; median % change in placebo was +7.2%; *p<0.05 ***p<0.001. Only subjects weighing >85 kg were enrolled in the 0.9 mg dose group, no body weight restrictions were implemented in other dose groups.

Table: Summary of Adverse Events

n, (%)	Placebo (N=22)	ALG-055009 0.3mg (N=20)	0.5mg (N=22)	0.7mg (N=20)	0.9mg (N=18)
Any TEAE	17 (77.3)	14 (70.0)	11 (50.0)	14 (70.0)	11 (61.1)
TEAE Leading to Study Drug Discontinuation	0	0	1[a] (4.5)	0	0
Serious AE	1[b] (4.5)	0	0	0	0
Grade 3 or higher TEAE	1[b] (4.5)	1[c] (5.0)	0	0	0
Gastrointestinal TEAEs	5 (22.7)	4 (20.0)	2 (9.1)	7 (35.0)	5 (27.8)
Diarrhea	5 (22.7)	1 (5.0)	0 (0.0)	2 (10.0)	2 (11.1)
Constipation	0 (0.0)	2 (10.0)	0 (0.0)	3 (15.0)	0 (0.0)
Nausea	1 (4.5)	2 (10.0)	0 (0.0)	0 (0.0)	1 (5.6)
Vomiting	1 (4.5)	1 (5.0)	1 (4.5)	0 (0.0)	0 (0.0)

TEAE = treatment emergent adverse event
a. Grade 2 worsening insomnia in a subject with pre-existing insomnia; b. Grade 3 hemangioma of bone; c. Grade 3 anemia assessed by the Investigator as not related to study drug in a subject with heavy menstrual bleeding and a history of polycystic ovary syndrome and heavy menstrual periods.

[8]
PHARMACOLOGICAL CHARACTERIZATION OF EA3571: A NOVEL DUAL INHIBITOR OF ENTEROPEPTIDASE AND TRYPSIN WITH LUMINAL ACTION FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Ayatoshi Andou, MS

Abstract Category: Experimental/Basic science, Liver Fibrosis, Non-humans

Background Information/Purpose – A previous report had identified dietary protein intake as a primary nutritional risk factor for MASH (Cell Metab. 2024 Nov 5; 36(11): 2437-48.). EA3571 is a novel dual inhibitor of enteropeptidase and trypsin with luminal action, and mimics the low protein diet condition by inhibiting the degradation and absorption of dietary protein. In addition, EA3571 has the potential to embody the effects of gastric bypass surgery by preventing the digestion of dietary nutrients in the small intestine of obese MASH patients. The aim of the following studies is to demonstrate the efficacy of EA3571 in MASH and to elucidate its pharmacological properties and mode of action.

Methods – The in vitro inhibitory activity of EA3571 against human enteropeptidase and trypsin activity was determined. Single oral dose studies were performed in normal mice to confirm the dietary protein degradation and hormonal changes. The effects of repeated oral doses of EA3571 were investigated in a high-fat, high-fructose and high-cholesterol (GAN) diet-induced mouse MASH model.

Results – The 50% inhibitory concentration values of EA3571 against human enteropeptidase, trypsin 1, 2 and 3 were 0.38, 0.37, 0.29 and 0.13 nmol/L, respectively. The inhibitory constant values were further calculated to be 0.083, 0.15, 0.15 and 0.056 nmol/L, respectively. The effect of EA3571 on elevated plasma hydroxyproline levels in normal mice following oral gelatin administration was assessed, confirming that luminal exposure of EA3571 inhibited intestinal degradation of dietary protein. In addition, EA3571 significantly increased plasma levels of GLP-1, PYY and FGF-21, hormones with potential therapeutic effects on MASH. Finally, repeated doses of EA3571 showed an ameliorative effects on various pathological parameters such as liver steatosis, inflammation and fibrosis, as well as on blood ALT, obesity and insulin resistance in the GAN diet-induced mouse MASH model.

Conclusions – In vitro studies show that EA3571 is a highly potent dual inhibitor of enteropeptidase and trypsin. EA3571 inhibited luminal proteolysis, allowing dietary proteins to reach the lower small intestine and promoting the secretion of hormones such as GLP-1 and PYY from the intestine. EA3571 also mimicked the 'effects of a protein-restricted diet' and promoted FGF-21 secretion from the liver, which may have anti-insulin resistance and fat-burning properties. EA3571 had completed a Phase 1 clinical trial as a new oral treatment for MASH.

[9]
FIRST-IN-HUMAN, PHASE 1 STUDY OF EA3571, WHICH IS A NOVEL DUAL INHIBITOR OF ENTEROPEPTIDASE AND TRYPSIN WITH LUMINAL ACTION, IN HEALTHY ADULT PARTICIPANTS

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Abstract Category: Therapeutic trials - MASH/liver fibrosis – Humans Clinical trial design

Background Information/Purpose – EA3571 is a novel dual inhibitor of enteropeptidase and trypsin with luminal action. EA3571 has the potential to embody the effects of gastric bypass surgery (GBS) by preventing the digestion of dietary nutrients in the small intestine of obese metabolic dysfunction-associated steatohepatitis (MASH) patients. EA3571 significantly improved liver fibrosis and obesity in a high-fat, high-fructose and high-cholesterol diet-induced MASH mouse model at 12 weeks. We assessed safety, pharmacokinetics and pharmacodynamics (PD) of EA3571 in a first-in-human phase 1 study in healthy adult participants (jRCT2051220036).

Methods – This study consisted of single ascending dose (SAD) parts, multiple ascending dose (MAD) parts and gelatin load test parts. In SAD parts, healthy adult participants received oral EA3571 (10 mg to 1200 mg) or placebo in fasted condition. In MAD parts, healthy adult participants received oral EA3571 (50 mg to 200 mg, three times/day) or placebo for 7days. In the gelatin load test parts, the inhibitory of EA3571 on enteropeptidase and trypsin in luminal side was assessed by measuring plasma hydroxyproline (Hyp) level after loading gelatin as a protein which has high content of Hyp.

Results – In the three parts, no serious TEAEs, severe TEAEs, or TEAEs leading to discontinuation of investigational products were observed. Moreover, there were no treatment related TEAEs with gastrointestinal disorders (eg. nausea). The plasma EA3571 concentrations decreased with $t_{1/2}$ less than 1 hour in SAD parts. No abnormal accumulation of EA3571 was observed in MAD parts. The elevation of plasma Hyp level by gelatin loading was suppressed by EA3571 in a dose-dependent manner. EA3571 administered in the morning continuously suppressed the elevation of plasma Hyp level by gelatin loading at lunch as well as that at breakfast. These results in gelatin load test parts suggested that EA3571 inhibited enteropeptidase/trypsin on the luminal side and that the inhibitory effect of EA3571 was sustained. In MAD parts, plasma total GLP-1 concentrations increased to higher levels after lunch and dinner in the EA3571 groups, and the increase was maintained longer compared to placebo group.

Conclusions – The results suggest that EA3571 has well-tolerated favorable safety profile and may improves MASH by embody the effects of GBS due to inhibiting enteropeptidase/trypsin on the luminal side in patients with MASH.

[10]
INTEGRATING DATA LIBRARIES AND MODELS FOR ENHANCED DECISION-MAKING IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS DRUG DEVELOPMENT: THE INSILICOTRIALS PLATFORM

Niccolò Totis[1], Giuseppe Pasculli[2], Chiara Nicolò[2], Fianne Sips[1], Pauline Bambury[2], Mario Torchia[2], Daniel Röshammar[2]

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Abstract Category: Clinical Trial Design

Background Information/Purpose – The InSilicoTrials platform is a modern, cloud-native, and modular web environment that allows users to build advanced analysis workflows by integrating diverse data sources and pharmacometrics models, streamlining and enhancing the accessibility of advanced analyses and simulations for drug development.= A comprehensive set of modeling methodologies are supported, including pharmacokinetic/pharmacodynamic (PKPD), quantitative systems pharmacology (QSP), exposure-response, and machine learning (ML) models.

Methods –The InSilicoTrials platform utilizes a broad array of Azure Cloud Services for secure, scalable, and efficient simulations. The platforms modular design enables seamless connections between models developed in different programming languages (NONMEM, R, Python, Matlab, etc), thereby facilitating the construction of complex modeling workflows.
These modelling workflows are integrated with modules for statistical analyses on input datasets and simulation outputs static and interactive visualizations, yielding insights into potential treatment effects and outcomes and clear, practical guidance for informed decision-making in drug development.
A module on the platform was developed for supporting metabolic dysfunction-associated steatohepatitis (MASH) study design and interpretation.

Results – The InSilicoTrials platform is demonstrated through its application in optimizing MASH clinical study designs. A model for fibrosis disease progression, describing the transition between fibrosis stages and mortality, was implemented on the platform [1]. We illustrate how the model can be used for clinical trial simulation of MASH studies to explore the impact of patient selection and better predict the corrected drug effect. By combining the disease progression model with drug specific PK/PD models in automatized workflows the platform offers a drug development tool both for technical users and the wider project teams .

Conclusions – 1In summary, the InSilicoTrials platform serves as a robust tool to facilitate complex simulations and analyses that maximize the extraction of meaningful insights from heterogeneous data sources, informing better decision-making in drug development while de-risking and optimizing financial investments.
References: [1] Knochel et al, A Markov model of fibrosis development in nonalcoholic fatty liver disease predicts fibrosis progression in clinical cohorts CPT Pharmacometrics Syst Pharmacol 2023 Dec;12(12):2038-2049

[11]
MONARCH: A PHASE 2B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF MIRICORILANT IN ADULT PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH)

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Abstract Category: Clinical Trial Design

Background Information/Purpose – Cortisol, a hormone that regulates metabolism and stress, has been implicated in the development and progression of MASH. Miricorilant, an orally delivered, nonsteroidal, selective glucocorticoid receptor modulator, may reduce hepatic steatosis by modulating cortisol activity and improving liver health. In a phase 1b multi-cohort, dose-finding trial (NCT05117489), adult patients (pts) with presumed MASH were treated with miricorilant 30 to 200 mg dosed daily or intermittently for 12 or 24 weeks (wks). Miricorilant 100 mg twice weekly had the best benefit-risk profile. At wk 12, the mean relative reduction in liver fat content (LFC) was −28.2% (standard deviation [SD]: 13.5), with a corresponding decline in liver enzymes (mean change from baseline: alanine aminotransferase, −4.0 [SD: 21.4]; aspartate aminotransferase, −6.0 [SD: 7.2]). This dose of miricorilant was safe, well-tolerated, and resulted in improved hepatic, lipid, and glycemic markers (Alkhouri et al. AASLD 2023). Consequently, twice-weekly miricorilant is being evaluated in the phase 2b MONARCH study (NCT06108219).

Methods – Adult pts (18–75 years) with LFC ≥8% by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) and risk factors for MASH (type 2 diabetes mellitus or metabolic syndrome) are being enrolled. Cohort A will include ≈120 pts with liver biopsy-confirmed MASH (NASH-CRN fibrosis stage 2 or 3). Cohort B will include ≈75 pts who have a liver biopsy result that does not meet the criteria for inclusion in Cohort A and a nonalcoholic fatty liver disease activity score (NAS) ≥3 and NASH-CRN fibrosis score of 1, or a NAS ≥2 and NASH-CRN fibrosis score of 2 or 3. Pts in Cohort A will be randomized 2:1 to miricorilant 100 mg or placebo twice weekly for 48 wks. Pts in Cohort B will be randomized 2:1 to miricorilant 100 mg or placebo twice weekly for 6 wks, followed by dose escalation to miricorilant 200 mg or placebo for 18 wks. Randomization will be stratified by type 2 diabetes status and fibrosis stage. The primary endpoint is change from baseline in LFC at wk 24, as assessed by MRI-PDFF. A key secondary endpoint in Cohort A is resolution of steatohepatitis and no worsening of liver fibrosis at wk 48, as assessed by biopsy. Other secondary and exploratory endpoints include safety, pharmacokinetics, and changes in liver enzymes, inflammatory markers, glycemic markers, and lipids.

Results/Conclusion – The MONARCH trial is currently enrolling.

Disclosures– Naim Alkhouri reports: grant/research support from 89bio, Akero Therapeutics, Arbutus Biopharma, AstraZeneca, BioAge, Boehringer Ingelheim, Bristol Myers Squibb, Corcept Therapeutics, CymaBay Therapeutics, DSM, Galectin Therapeutics, Genentech, Genfit, Gilead Sciences, Healio, Hepagene Therapeutics, Intercept Pharmaceuticals, Inventiva Pharma, Ionis Pharmaceuticals, Ipsen, Lilly, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Noom, NorthSea Therapeutics, Novo Nordisk, Perspectum, Pfizer, and Zydus Pharmaceuticals.
Nirupama Esther Jerome reports nothing to disclose.
Eric Lawitz reports: researcher for 89Bio Inc., Akero Therapeutics, Alnylam Pharmaceuticals Inc., Amgen, Astrazeneca, Boehringer Ingelheim, Bristol Myers Squibb, Corcept Therapeutics, COUR Pharmaceuticals, CymaBay Therapeutics, Eli Lilly and Company, Enanta Pharmaceuticals, Enyo Pharma, Exalenz Bioscience, Galectin Therapeutics, Galmed Pharmaceuticals, Genfit, Gilead Sciences, GlaxoSmithKline, Hanmi Pharmaceuticals, Hightide Biopharma, Intercept Pharmaceuticals, Inventiva, Ipsen, Janssen Pharmaceuticals, Madrigal Pharmaceuticals, Merck & Co., NGM Biopharmaceuticals Inc., NorthSea Therapeutics, Novartis, Novo Nordisk Inc., Organovo, Poxel Co., Regeneron, Sagimet Biosciences, Takeda, Terns Pharmaceuticals, Viking Therapeutics, and Zydus Pharmaceuticals; speaker for AbbVie, Gilead Sciences, Intercept, and Madrigal; consultant for 89Bio Inc., AstraZeneca, Boehringer Ingelheim, Corcept Therapeutics, Eli Lilly and Company, Merck & Co., Novo Nordisk Inc., Organovo, Regeneron, and Sagimet Biosciences.
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Nadege Gunn reports: nothing to disclose.
Daniel Santillano reports: nothing to disclose.
Iulia Cristina Tudor reports: employed by and own stock in Corcept Therapeutics.
Joseph M. Custodio reports: employed by Corcept Therapeutics.
Rafael Mayoral Monibas reports: employed by Corcept Therapeutics.
Aprille Espinueva reports: employed by Corcept Therapeutics.
Kavita Juneja reports: employed by Corcept Therapeutics.
William Guyer reports: employed by Corcept Therapeutics.
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[13]
ICURRENT STATE OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) CARE DELIVERY, INCLUDING KEY BARRIERS, AND BEST PRACTICES: A SURVEY ANALYSIS

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Abstract Category: Disease Management of MASH/Liver Fibrosis Patients (including comorbidities)

Background Information/Purpose – Although Metabolic Dysfunction-Associated Steatohepatitis (MASH), formerly known as NASH, has become an increasingly prevalent chronic disease in the United States, the lack of early identification and standardized care pathways leads to underdiagnosis and poor management of the disease. The objective was to examine key gaps impacting MASH screening, diagnosis, and care delivery cited by population health decision makers and providers.

Methods –Two online double-blind surveys were developed and implemented from May to August 2024. The surveys were identical except for their final sections. One survey focused on clinical points and targeted clinicians in hepatology, gastroenterology, endocrinology, and primary care (N=106); the other focused on population health and targeted administrative and population health leaders (N=62). Respondents represented a mix of institution types, with the majority (63%) working at not-for-profit academic medical centers. An institutional review board exemption was issued.

Results- All respondents indicated that MASH is underprioritized compared to other chronic conditions. Twenty-five percent of respondents indicated that their organization offers preventative care programs for MASH, while over 70% cited existing programs related to obesity, cardiovascular disease, and diabetes. Only 42% of respondents have a standardized referral process for MASH patients at their institution. Respondents also cited that available quality metrics focus primarily on specialist referral rates for patients with elevated FIB-4 scores. The most common first-line non-invasive diagnostic used amongst respondents to identify high-risk patients for advanced fibrosis is FIB-4. Over 50% of respondents indicated that enhanced education, for both primary care providers and patients, was the top resource needed to better manage MASH populations. Respondents also indicated the impact of multidisciplinary care models on improved patient diagnoses and wait times.

Conclusions– Both clinical and administrative leaders indicated that MASH care delivery needs improvement across the care continuum. Enhanced patient and provider educational resources, particularly for primary care, are one of the biggest areas of need related to MASH. Additional examples given for areas of improvement were EHR-embedded clinical decision support tools, standardized care pathways, and quality metrics.

[19]
MAINTENANCE THERAPY WITH GLP-1 RECEPTOR AGONISTS DOES NOT IMPACT THE CLEARANCE OF ORALLY ADMINISTERED ISOTOPES OF UNCONJUGATED CHOLATE

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Abstract Category: Diagnostic procedures for MASH/liver fibrosis

Background Information/Purpose –Glucagon-like-peptide-1 receptor agonists (GLP-1 RAs) are prescribed for obese and diabetic patients with MASLD/MASH and may slow gastric emptying. A liquid solution of d4-cholate (d4-CA) is administered in the HepQuant SHUNT and DuO tests to measure liver function and portal-systemic shunting. If GLP-1 RAs slow gastric emptying of the d4-CA solution, the clearance curve would shift, potentially compromising accuracy of the HepQuant SHUNT and DuO test. For these reasons, we compared the characteristics of clearance of orally administered d4-CA between patients on maintenance GLP-1 RAs versus patients not taking these medications.

Methods –The patients were enrolled in the SHUNT-V study. Forty mg of d4-CA was administered as an oral solution, 20 mg 13C-CA was injected intravenously, and blood was sampled at baseline and at 5, 20, 45, 60, and 90 min post-dose. Serum d4- and 13C-CA concentrations were measured by LC-MS/MS, and AUCs were calculated. The test results were compared between subjects on maintenance GLP-1 RA treatment (n=32) and subjects not taking them (n=243).

Results – The GLP-1 RAs (n subjects) were liraglutide (12), dulaglutide (12), semaglutide (6), exenatide (3), and dulaglutide plus exenatide (1). One subject on semaglutide had an invalid test due to low d4-CA concentrations. Clearance curves of d4-CA were similar between subjects on GLP-1 RAs and subjects not taking them. The time-dependent pattern of absorption, peak concentration, and elimination, as reflected in the serum concentrations of d4-CA was similar. The AUC of d4-CA was significantly lower in subjects taking GLP-1 RAs (p=0.03) suggesting a potential impact on gastric emptying of the d4-CA solution. But, the AUC of 13C-CA was similarly decreased (p=0.02), and the prevalence of large varices was lower. In total, the results do not support an effect of GLP-1 RAs on gastric emptying d4-CA, but rather suggest that patients on GLP-1 RAs had less severe hepatic disease.

Conclusions – This analysis demonstrates that there is little to no impact of maintenance GLP-1 RAs on the clearance of an orally-administered d4-CA liquid solution. However, because the effect of GLP-1 RAs on gastric emptying may vary with type of GLP-1 RA and duration of GLP-1 RA treatment, and some may have dual (GIP) or triple (GIP, amylin) effects, we advise holding GLP-1 RAs (and other drugs that slow gastric emptying) for 7 days prior to administering the HepQuant tests.

Disclosures: MPM is a paid consultant for HepQuant, LLC. GTE is an employee and equity member of HepQuant, LLC. MPM and GTE have issued and pending patents. This abstract has been presented as a poster at AASLD 2024.

[20]
THE ORAL CHOLATE CHALLENGE TEST IDENTIFIES THE MASH PATIENTS WITH ≥F3 FIBROSIS WITH GREATEST HEPATIC IMPAIRMENT WHO SHOW THE MOST BENEFIT FROM SHORT-TERM RENCOFILSTAT THERAPY

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Abstract Category: Diagnostic procedures for MASH/Liver fibrosis

Background Information/Purpose –Rencofilstat (RCF) is an antifibrotic cyclophilin inhibitor targeting MASH-related fibrosis. In MASH, liver dysfunction and altered portal physiology precede clinical complications. HepQuant DuO is a non-invasive, blood-based test of liver function, portal circulation, and portal-systemic shunting. In this study DuO quantified effects of RCF on liver function and physiology.

Methods –70 subjects with MASH and AGILE 3+ >0.53 (≥F3 fibrosis) were randomized 1:1:1 into 3 RCF treatment arms (75, 150, 225 mg/d) and underwent HepQuant SHUNT tests at baseline and days 60 and 120. Subjects were administered 40 mg of labeled cholate (CA) orally, and blood CA concentrations analyzed at 20 and 60 min for these DuO parameters: systemic and portal hepatic filtration rates (HFRs), disease severity index (DSI), hepatic reserve (HR), and portal systemic shunt (SHUNT%). Changes from baseline to 60 and 120 days were analyzed, and numerous other MASH non-invasive assessments were also collected.

Results – Baseline characteristics revealed an advanced MASH population (Agile 3+ 0.73±0.15). Among subjects, 30.4% had significant hepatic functional impairment (DSI >18.3), 37.7% had increased portal-systemic shunting (SHUNT% >27%), and 23.2% had both. DuO results with 225 mg RCF revealed significant reductions after 60 and 120 days in DSI (−1.34, p=0.022; −1.61, p=0.019) and SHUNT% (–2.24%, p=0.043; –2.28%, p=0.094) in paired analysis. Improved liver function (reduction of ≥2 DSI units) occurred in 10/18 subjects (55.6%) in the 225 mg group after 120 days (p=0.055). DuO test parameters showed the greatest improvement in subjects with the greatest baseline dysfunction (DSI >18.3) after 120 days with 225 mg RCF, with significant reductions in both DSI (–2.59, p=0.005) and SHUNT% (–4.75%, p<0.001). Additionally, there was a clear dose response in many of the other non-invasive assessments.

Conclusion: RCF (225 mg) was associated with reduction in DSI and SHUNT% after 120 days, suggesting improvement in effective hepatic perfusion possibly due to fibrosis remodeling given RCF's anti-inflammatory and antifibrotic properties. These changes may be most effective in patients with more severe liver impairment. These results demonstrate the successful use of HepQuant DuO to assess hepatic function and the promise of RCF as a potential MASH treatment in patients with advanced fibrosis.

Disclosures: SAH was a paid consultant for Hepion Pharmaceuticals, Inc. PM, TH, DU, and RF were previously employees and shareholders of Hepion Pharmaceuticals, Inc. MPM is a paid consultant for HepQuant, LLC. GTE is an employee and equity member of HepQuant, LLC. MPM and GTE have provisional patents pending. This abstract has been presented as a poster at AASLD 2024.

[22]
THE ORAL CHOLATE CHALLENGE TEST DEFINES LIKELIHOOD OF LARGE ESOPHAGEAL VARICES IN AN OVERWEIGHT AND OBESE US POPULATION

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Abstract Category: Diagnostic procedures for MASH/Liver fibrosis

Background Information/Purpose – Although well-validated in chronic viral hepatitis, the accuracy of transient elastography (TE) may be compromised in populations with high prevalence of obesity and MASLD/MASH. In the US-based SHUNT-V study, prevalences of overweight, obesity, and MASLD/MASH were 85%, 65%, and 50%, respectively. In this study, we evaluated the Disease Severity Index (DSI) from the oral-only HepQuant DuO test in the diagnostic performance for LEVs.

Methods –Subjects were enrolled in two prospective studies linking HepQuant test results to endoscopic (EGD) findings. DuO test parameters were quantified from 20- and 60-min concentrations of orally administered d4-cholate (40 mg) (McRae et al., 2024). The SHUNT-V study enrolled 238 subjects with CP A cirrhosis (Hassanein et al., 2024). We added 217 subjects with prospective HepQuant and EGD data (HALT-C cohort) to expand the sample size and improve estimates of diagnostic performance. We evaluated DSI cutoffs for ruling out LEVs using a minimum acceptable sensitivity of ≥95% (miss rate <5%). The diagnostic performance was evaluated in terms of AUROC, sensitivity, and specificity. We determined the percentage of subjects who would have avoided EGD and miss rates for LEVs among those who avoided EGD. We normalized DSI according to subject body weight and by estimated blood volume.

Results – DSI score from DuO was an accurate predictor of LEVs across all body sizes. Overall, DSI at the cutoff of 18.3 to rule out LEVs had sensitivity 98% (95% CI, 89–100%), would have missed one LEV case (2.0%), and would have prevented 188 unnecessary EGDs (41.3%). AUROCs (95% CI) were comparable across body size groups. For the whole group, DSI normalized by estimated blood volume had the same sensitivity, greater specificity (48% vs. 46%), and would have prevented 7 (1.6%) more EGDs than DSI normalized by body weight. In obese individuals, specificity improved from 31% to 40% when normalizing DSI by blood volume.

Conclusion: HepQuant DuO predicts the likelihood of finding LEVs on endoscopy in a population characterized by overweight, obesity, and enriched in MASLD/MASH. Normalizing DSI by estimated blood volume may improve the specificity of the test in obese individuals. The simplicity of DuO test administration will likely enhance its implementation by healthcare providers and acceptance by patients. HepQuant DuO may be a useful aid in the decision to avoid or proceed with endoscopic screening or surveillance of LEVs.

Disclosures: MPM is a paid consultant for HepQuant, LLC. GTE is an employee and equity member of HepQuant, LLC. MPM and GTE have issued and pending patents. This abstract has been presented as a poster at AASLD 2024.

[23]
PILOT STUDY OF A MODEL BASED ON NONINVASIVE ASSESSMENTS OF PORTAL-SYSTEMIC SHUNTING (HEPQUANT DUO), HEPATIC FIBROSIS (FIBROSCAN), AND SPLENIC CONGESTION (PLATELET COUNT) FOR ACCURATE PREDICTION OF PORTAL HYPERTENSION AND CLINICALLY SIGNIFICANT PORTAL HYPERTENSION

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Abstract Category: Diagnostic Procedures for MASH/Liver fibrosis

Background Information/Purpose – Portal hypertension (PH), particularly clinically significant PH (CSPH), is associated with portal-systemic shunting and risk for varices and clinical decompensation. HepQuant tests quantify liver function and portal-systemic shunting, and predict risk for PH and CSPH (Wieland, 2022). A dual sample oral dose version (HepQuant DuO) may have the greatest clinical utility due to ease of administration (McRae, 2024). In this study, we used HepQuant DuO with liver stiffness by FibroScan (LSM) and platelet count to explore the noninvasive prediction of PH and CSPH.

Methods –The model for predicting PH and CSPH was defined from 28 subjects enrolled in an NIH NIDDK study of fibrotic stages of chronic hepatitis C (NCT02400216). All subjects underwent standard laboratory tests, liver biopsy, portal pressure measurement, and HepQuant testing. HepQuant DuO generates a Disease Severity Index (DSI), which is a measure of global liver health, and quantifies portal systemic shunting (SHUNT%). Portal pressure was measured via percutaneous transhepatic cannulation of the portal vein, and stage of liver fibrosis was determined from simultaneously obtained liver biopsy (METAVIR) and elastography (FibroScan). Univariate and multivariate logistic regression and AUROC analyses were used to evaluate and compare models for predicting PH and CSPH.

Results – Fifteen subjects had PH and 9 had CSPH. CSPH was found in none of the 11 subjects with Stage 1 fibrosis, 1 of 4 with Stage 2 fibrosis, 1 of 2 with Stage 3 fibrosis, and 7 of 11 with Stage 4 fibrosis. In predicting PH, logistic regression models with SHUNT%, LSM, and platelet count yielded AUROCs of 0.995 (0.938–1.000, $p<0.0001$). Similarly in predicting CSPH, AUROCs were 0.947 (0.719–1.000, $p<0.001$).

Conclusion: The results of this pilot study demonstrate that noninvasive models incorporating DuO test parameters, with other commonly used noninvasive assessments, can predict PH and CSPH with near perfect accuracy (AUROCs ~1.00 for PH and ~0.95 for CSPH). Further validation is planned, and if these findings are confirmed, the DuO model could more accurately define the patient with either PH or CSPH. In addition to its clinical utility, the HepQuant DuO model may be useful in enrichment and stratification of potential subjects planned for enrolment in clinical trials of antifibrotic drugs being studied for PH.

Disclosures: MPM is a paid consultant for HepQuant, LLC. GTE is an employee and equity member of HepQuant, LLC. MPM and GTE have patents pending. This abstract has been presented as a poster at AASLD 2024.

[24]

ASSOCIATION BETWEEN FIBROSIS-4 INDEX AND MAJOR ADVERSE LIVER OUTCOMES IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS: A RETROSPECTIVE COHORT STUDY

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Abstract Category: Clinical epidemiology – MASH/liver fibrosis

Background Information/Purpose – Metabolic dysfunction-associated steatohepatitis (MASH) is a chronic condition that involves hepatic steatosis, inflammation, and ballooning, with or without fibrosis. The extent of fibrosis is considered the strongest predictor of major adverse liver outcomes (MALO). Fibrosis-4 (FIB-4) index is a non-invasive test that is used to estimate the risk of advanced fibrosis. This study aims to estimate the risk of developing MALO in patients with MASH at different levels of FIB-4.

Methods –This retrospective cohort study used Optum's de-identified Clinformatics® Data Mart Database to identify adult patients (≥18 years) newly diagnosed with MASH (index date) from 10/01/2016 to 09/30/2022. The FIB-4 score within ±90 days of the index date was calculated, and each patient was categorized into low (<1.30), indeterminate (1.30-2.67), or high (>2.67) risk group. The composite outcome, MALO (defined as any occurrence of cirrhosis or its complications, hepatocellular carcinoma [HCC], or liver transplant [LT]) and its individual events were assessed during follow-up. Crude incidence rate ratios (IRR) and Kaplan-Meier estimates of MALO events (composite and individual) were calculated at 6, 12, 18, and 24 months.

Results – Among 9,592 patients with MASH (mean follow-up = 28.6 months), 4,835 (50.4%), 3,193 (33.3%), and 1,564 (16.3%) had a low, indeterminate, and high FIB-4 score, respectively. At 2-year follow up, patients with high and indeterminate FIB-4 scores were 7 times (IRR: 6.98; 95% confidence intervals [CI]=5.84, 8.36), and 2.4 times (IRR: 2.35; 95% CI=1.95, 2.83) more likely to have a MALO compared to patients with low FIB-4 scores, respectively. Similarly, patients with a high FIB-4 score were more likely to experience cirrhosis (IRR 7.19; 95% CI= 6.01, 8.63), HCC (IRR 5.61; 95% CI= 2.26, 14.69), and LT (IRR 14.42, 95% CI= 2.88, 139.39) compared to the low score group. Results were significantly higher for the indeterminate risk vs. low risk group for cirrhosis (IRR: 2.40; 95% CI= 1.99, 2.90), but not for HCC (IRR: 1.32; 95% CI= 0.44, 3.86); and LT (IRR: 2.98; 95% CI= 0.43, 32.92). Similar trends in the analyses of MALO events were observed across the 6-, 12-, and 18-month follow-up periods (Table).

Conclusion: Patients with high FIB-4 scores had a significantly higher risk of MALO events compared to patients with low FIB-4 scores. Treatments that improve fibrosis in patients with MASH have the potential to delay the onset of adverse liver outcomes.

Table. Incidence Rate Ratios of MALO Events in Patients with MASH by FIB-4 Risk Categories at 6,12, 18, and 24 Months

Time period	Indeterminate vs. Low Risk		High vs. Low Risk	
	IRR	95% CI*	IRR	95% CI*
6 months	2.66	2.27, 3.12	8.07	6.95, 9.40
12 months	2.42	2.06, 2.84	7.36	6.33, 8.59
18 months	2.43	2.05, 2.89	7.14	6.06, 8.43
24 months	2.35	1.95, 2.83	6.98	5.84, 8.36

*Exact binomial distribution was used to calculate 95% confidence intervals for incidence rate ratios.
IRR: Incidence Rate Ratios; CI: Confidence Intervals

[25]

Risk of Major Adverse Liver Outcomes in Patients with Metabolic Dysfunction-Associated Steatohepatitis: A Large Population-Based Retrospective Cohort Study

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Abstract Category: Clinical epidemiology – MASH/liver fibrosis

Background Information/Purpose – Patients with metabolic dysfunction-associated steatohepatitis (MASH) are at increased risk for major adverse liver outcomes (MALO). However, research on the magnitude of this association in real-world settings is scarce. This study aimed to determine the extent to which patients with MASH have an increased risk for MALO compared to patients without MASH.

Methods –In this retrospective cohort study conducted using Optum's de-identified Clinformatics® Data Mart Database, we identified patients (≥18 years) with MASH, defined as having ≥2 outpatient claims (≥30 days apart) or ≥1 inpatient claim with ICD-10 code K75.81 (10/2016-09/2022). Exact matching on age (±1 year), sex, region of residence, health plan type, and index year was conducted to identify patients without MASH in a 1:1 ratio from the same database. Patients required 6 months continuous enrollment pre-index (baseline) and ≥3 months follow-up (unless death occurred), until end of enrollment or study end (12/31/2022). MALO was defined as any evidence of cirrhosis (or its complications), hepatocellular carcinoma (HCC), or liver transplant (LT). Kaplan-Meier survival rates were estimated, and the risk of MALO was analyzed using a Fine and Gray model accounting for competing risk of death. Subgroup analyses were conducted stratified by type 2 diabetes status and age group.

Results – In the matched cohort (n=26,301 pairs), patients had a mean age of 59.0 (13.7) years, with 56.3% being female and 52.3% having commercial insurance. Mean (SD) follow-up was 2.4 (1.6) and 1.9 (1.5) years for patients with and without MASH, respectively. Over the follow-up period, MALO occurred more frequently in patients with MASH (116.8 vs. 15.5 events per 1,000 person-years; incidence rate ratio [IRR]=7.55, 95% CI: 7.00-8.15) than in those without MASH. Patients with MASH also had significantly higher rates of cirrhosis (IRR: 7.85; 95% CI: 7.26-8.49), HCC (5.07; 3.94-6.51), and LT (18.42; 7.53-45.09) compared to those without MASH. After adjusting for baseline confounders, the risk for MALO remained significantly higher (adjusted hazard ratio: 6.78; 95% CI: 6.27-7.34) among patients with MASH compared to those without MASH. Results were similar in the subgroup analyses (Table).

Conclusion: Patients with MASH demonstrated a sevenfold higher risk for MALO than those without MASH. This highlights the significant clinical burden of MASH, underscoring the need for enhanced early detection and therapeutic strategies.

Table. pg 18

Table. Fine and Gray Regression Model for MALO Accounting for Competing Risk of Death in Patients With and Without MASH in Full Sample and by Type 2 Diabetes Status and Age Group				
Population	**Hazard* ratio**	**Lower 95% CI**	**Upper 95% CI**	**P value**
Full sample	6.78	6.27	7.34	<0.001
Patients with Type 2 Diabetes	5.37	4.8	6.01	<0.001
Patients without Type 2 Diabetes	7.69	6.92	8.56	<0.001
Patients Aged 18-64	8.69	7.51	10.05	<0.001
Patients Aged 65+	6.51	5.94	7.13	<0.001
*Adjusted for race/ethnicity, Charlson Comorbidity Index category, Diabetes Complications Severity category, presence of medication use (insulin, anticoagulants, antihypertensives, antihyperlipidemics), and baseline				

[26]
Velacur's VDFF outperforms FibroScan CAP in assessment of liver steatosis in a large cohort of MASLD and MASH patients

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Clinical area: Diagnostic Procedures

Abstract Category: Diagnostic Procedures - MASH/Liver Fibrosis

Background Information/Purpose –As MASLD and MASH therapies continue to be developed, measuring liver fat is becoming one of the most important predictors of longer-term patient response. Velacur is a point of care ultrasound device, which recently added the measurement of Velacur Determined Fat Fraction (VDFF) as an estimate of MRI-PDFF. VDFF combines ultrasound data parameters, specifically quantitative measures of attenuation and backscatter. This retrospective study aims to examine the accuracy of Velacur values to MRI-PDFF in a large cohort of patients from the MAESTRO-NAFLD-Open-Label-Extension (MAESTRO-NAFLD-OLE) study.

Methods:
Patients at 13 sites in the MAESTRO-NAFLD-OLE study were included into this retrospective analysis. Data was collected between Aug 2021 and May2024. All visits, during which a Velacur imaging scan was performed that passed the subjective quality assurance metrics, were analyzed. Patients received an MRI-PDFF and Velacur at Day 1, Week 16 and Week 52, and a FibroScan at Day 1 and Week 52. Each visit data pair was considered separately.
Patients with paired Velacur, or FibroScan, and MRI-PDFF measurements were used to analyze the correlation between ultrasound and MRI fat measures and the accuracy (AUROC) of the detection of 8%, 12% and 20% fat by MRI-PDFF.

Results – 1074 visits were conducted with Velacur, for this analysis those visits without MRI-PDFF, or sufficient Velacur quality were removed. 428 paired Velacur and 307 pair Fibroscan exams were assessed.
The correlation coefficient between MRI-PDFF and VDFF was 0.67 [0.62 – 0.72] for all patients with a paired measure, a MRI-PDFF cutoff of more than 8% had an AUROC of 0.85 for VDFF. MRI-PDFF correlation with Velacur attenuation (ACE) was 0.59 [0.52 – 0.65] or FibroScan CAP was 0.51 [0.42 – 0.59]. The correlation of the two stiffness measures to MRE results were not significantly different (0.72 [0.65-0.78] for VCTE vs 0.67 [0.59-0.73] for Velacur). Table 1 summarizes the AUROC of VDFF, ACE and CAP in all visits with a paired MRI and ultrasound result.

Conclusion: This retrospective analysis of patients in the MAESTRO-NAFLD-OLE study demonstrates a strong agreement of Velacur VDFF with MRI-PDFF in the assessment of hepatic steatosis. Implementation of cutoffs of more than 8% indicates a high sensitivity for VDFF compared to CAP in the detection of fat fraction. Velacur has the ability to accurately estimate liver fat in this cohort of patients with MASLD or MASH.

Table 1: Summary of AUROC values for ultrasound-based liver fat estimates

	CAP AUROC [95% CI]	ACE AUROC [95% CI]	VDFF AUROC [95% CI]
≥ 8% MRI-PDFF	0.79 [0.73, 0.83]	0.80 [0.75, 0.84]	0.85 [0.81, 0.88]
≥ 12% MRI-PDFF	0.74 [0.68, 0.80]	0.82 [0.77, 0.85]	0.86 [0.82, 0.89]
≥ 20% MRI-PDFF	0.75 [0.67, 0.82]	0.85 [0.79, 0.90]	0.87 [0.81, 0.91]

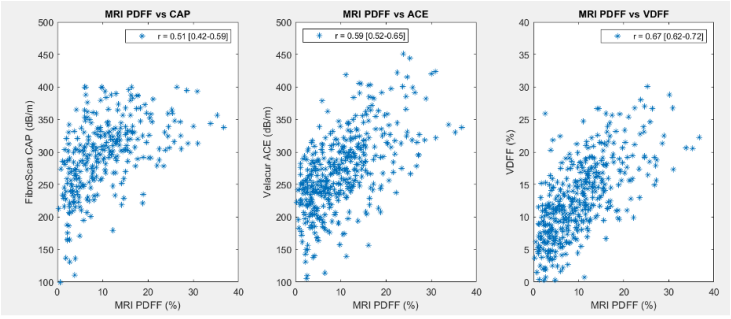

Figure 1: Correlation between MRI-PDFF and CAP, ACE and VDFF

[27]

The utility of noninvasive tests, VCTE, FIB-4 and LIVERFASt, in the initiation and monitoring of the therapy with TNR-beta agonist (resmetirom) in MASH patients

Jeevin Singh Sandhu and Parvez Mantry

Abstract Category: Diagnostic Procedures - MASH/Liver Fibrosis

Background Information/Purpose –Resmetirom, a THR-beta agonist, was recently approved by the FDA for non-cirrhostic MASH with fibrosis, in combination with diet and exercise, in the US. Previous studies have shown that resmetirom led to a significant decrease in liver fat after 12 and 36wks of treatment and this effect was maintained over 52 weeks with continued treatment.(Harrison S, Lancet 2019 and NatMed 2023) More than one in four patients can achive improvement in MASH without worsening fibrosis and conversely, improvement in fibrosis by at least one stage without worsening the NAFLD activity score. (Harrison, N Engl J Med 2024; Raja A, Ann Med Surg 2024). Clinical evidence indicates that resmetirom accelerates extracellular matrix (ECM) degradation by modulating matrix metalloproteinases (MMP) and their tissue inhibitors with anti-fibrotic/anti-inflammatory potential effects. LIVERFASt test is a new blood-based non-invasive device that asseses the severity of fibrosis, activity, and steatosis, that has a potential in monitoring patients as it uses blood-based inputs - the MMP-inhibitor, alpha2-macroglobulin, the oxidative stress regulator GGT- that interferes with resmetirom action mechanisms.

Aims. 1/ To assess non-invasively the interest in NITs (VCTE, FIB-4 and LIVERFASt) in initiating and monitoring patients ongoing resmetirom therapy 2/ To assess non-invasively the fibrosis regression rate (FRR) and the improvement in steatohepatitis during therapy (4, 8 and 12 months) and at the end of follow up (EOF) 3/ To evaluate the correlation with clinical outcomens and identify factors associated with significant improvement.

Methods- XX patients had repeated measurements of LIVERFASt, VCTE and FIB4 at baseline , 4, 8 , 12 mts and EOF of resmetirom tratment with xx mg. More information will be provided during the AASLD liver meeting.

LIVERFASt test is a new non-invasive device is a software-only system that employs a proprietary algorithm which generates two-decimal scores from 0.00 to 1.00, proportional to the severity of fibrosis, activity, and steatosis based on a standard set of inputs (blood-based and biomarkers). FRR was assesed between baseline and each follow up. A significant change in fibrosis using LIVERFASt was considered 0.10 improvement in the score, xx for VCTE and 0.30 in FIB4. Statistics included repeated measurements ANOVA, time dependent statistics cox Mantel hazard ratios (HR, 95%CI) and, logrank for the comparitions between groups that achieved a significant improvement and that do not.

Results- A total of XX patients (% male, age, BMI, mean ALT , mean VCTE, mean FIB4, % F2, % F3) are include with R therapy and xx(%) had a first assessment at 4 months.
% of pts concur for fibrosis staging as per VCTE and LIVERFASt and % as per VCTE and FIB4.
The mean (se) scores between baseline and 4mts-assessment were: for LIVERFASt xx vs xx (p value), VCTE xx vs xx (p value) and FIB4.
X/xx (%)pts had a significant improvment with both LIVERFASt and VCTE (logrank p value at 4 mts). The cox Mantel hazard ratios (HR, 95%CI) were xx (xx-xx) vs xx(xx-XX) in the groups that achieved improvement compared to the group that do not a. The main factors predictive of improvement at 4mts in multi-variate ananalysis were: baseline age, BMI, steatosis, CAP, VCTE, LIVERFASt FASetc.

Conclusion- Initiation of resmetirom therapy based on non-invasive assessment of patients using LIVERFASt and VCTE is efficient and allows further non-invasive monitoring.

[29]

Use of non-invasive tests to diagnose and follow NASH with liver fibrosis patients treated with resmetirom

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Abstract Category: Diagnostic Procedures - MASH/Liver Fibrosis

Background Information/Purpose –MAESTRO-NASH (NCT03900429) is an ongoing 54-month, randomized, double-blind, placebo-controlled Phase 3 trial evaluating the efficacy of resmetirom in patients with biopsy-confirmed nonalcoholic steatohepatitis (NASH/MASH) and fibrosis. 966 patients with biopsy-confirmed NASH were randomized 1:1:1 to resmetirom 80 mg, resmetirom 100 mg, or placebo administered once daily. Dual primary endpoints at Week 52 were achieved with both resmetirom 80 mg and 100 mg: NASH resolution with no worsening of fibrosis (NR) or ≥1-stage improvement in fibrosis with no worsening of NAS (FI). Both Week 52 liver biopsy endpoints, NR and FI, were achieved. Resmetirom was recently approved for the treatment of adult patients with noncirrhotic NASH and liver fibrosis consistent with F2 to F3 stages. Accuracy of NASH/fibrosis diagnosis and follow-up of resmetirom treated patients long-term using real-world, readily available non-invasive testing were assessed.

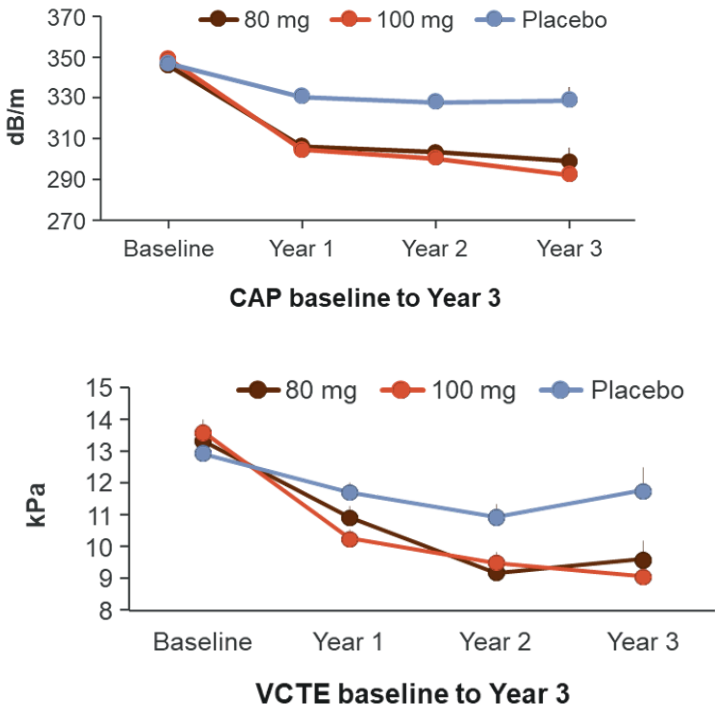
Methods- Machine learning models evaluated the relative importance of MAESTRO patients' intrinsic characteristics and screening/baseline biomarkers in 1247 patients who had F0-F4 on liver biopsy. The Random Forrest (RF) model was selected due to its predictive performance. For this model, only readily available tests including FibroScan, ELF and standard blood chemistries were used to determine the accuracy in diagnosing NASH patients consistent with F2 to F3. Long-term effects of resmetirom on non-invasive tests and biomarkers out to 3 years post randomization were evaluated.

Results- In the F2 to F3 population (n=888) FibroScan VCTE was 12 (10,15) median kPa (Q1, Q3) and ELF 9.7 (9.2, 10.4). Using 23 baseline clinical characteristics, standard labs, FibroScan and ELF, the random forest model determined that the most important markers that distinguished F2 to F3 from either F0/1 or F4, in order, were FibroScan VCTE, platelets, FIB-4, FAST and ELF. The AUC (SD) for separation from F0/F1 or F4 were 0.76 (0.03) and 0.90 (0.03), respectively. 58% of F2 to F3 were correctly predicted to be F2/F3; 26% were incorrectly predicted to be F0/F1 and 16% were incorrectly predicted to be F4. Of F4 patients, 72% were correctly predicted to be F4 and 19% were predicted to be F2/F3. The addition of MRE/MRI-PDFF increased diagnostic accuracy for F2/F3 to 68% and F4 to 81%. Resmetirom showed improvement relative to placebo on multiple responses at Week 52 including MRI-PDFF (the most predictive of a biopsy response), liver enzymes, lipids and FibroScan CAP and VCTE. Resmetirom responses on liver enzymes, lipids and FibroScan (Figure) were durable/increased at Years 2 and 3 relative to placebo.

Conclusion- Reasonably accurate identification of NASH F2/F3 patients was achieved with FibroScan VCTE, ELF and readily available blood tests. F4 patients were effectively ruled out. Long term follow-up of resmetirom patients with noninvasive tests showed durability of responses relative to placebo.

Figure pg. 20

Figure



[30]

Impact of resmetirom on statin pharmacokinetics safety in Phase 1 and 3 studies; safety and efficacy of resmetirom in patients on statins in MAESTRO-NASH

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Abstract Category: Disease Management of MASH/Liver Fibrosis Patients (including comorbidities)

Background Information/Purpose –Resmetirom was approved by FDA and is indicated for treatment of adults with non-alcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3). In MAESTRO-NASH, 49% of enrolled patients were taking statins, including 13% on high intensity statins (rosuvastatin 20 mg; atorvastatin 40 mg), and 36% on moderate or low intensity statins; therefore, the study population included approximately 95% of the statin dose regimens in use by NASH patients.

Methods- Drug interaction studies of resmetirom with commonly prescribed statins were performed in Phase 1 healthy volunteers. Statin levels were measured in MAESTRO-NAFLD-1, a non-invasively diagnosed NASH population. In MAESTRO-NASH, liver enzymes were assessed in patients on statins and not on statins; assessments of common statin AEs were assessed in MAESTRO-NASH; safety was assessed in patients in MAESTRO-NASH according to statin therapy at baseline; and safety and responses were assessed as a function of statin therapy.
We analyzed data from the Phase 1 pharmacokinetic studies and the Phase 3 study to evaluate the potential impact of co-administration of resmetirom and statins on statin pharmacokinetics in healthy subjects and patients with NASH and fibrosis. Safety and efficacy by statin dose in Phase 3 were also evaluated.

Results- Simvastatin: Simvastatin (an OATP1B1 and OATP1B3 substrate) Cmax increased 1.4-fold and area under the curve (AUC) 1.7-fold following concomitant use of a single oral dose of simvastatin (20 mg) with resmetirom at steady state (100 mg/day) in healthy subjects. Rosuvastatin: Rosuvastatin (BCRP, OATP1B1, and OATP1B3 substrate) AUC 1.8-fold following concomitant use of a single oral dose of rosuvastatin (10 mg) with 200 mg resmetirom at steady state (two times the highest recommended dosage) in healthy subjects.
Pravastatin: Pravastatin (OATP1B1 and OATP1B3 substrates) Cmax increased 1.3-fold and AUC 1.4-fold following concomitant use of a single oral dose of pravastatin (40 mg) with resmetirom at steady state (100 mg/day) in healthy subjects. Atorvastatin: Atorvastatin (BCRP, OATP1B1, and OATP1B3 substrates) Cmax was unchanged and AUC increased 1.4-fold following concomitant use of a single oral dose of atorvastatin (20 mg) with resmetirom at steady state (100 mg/day) in healthy subjects. Statin PK assessment in MAESTRO-NASH demonstrated that the levels of statins were within the range of normal variability. Assessment of statin safety parameters including muscle AEs and liver AEs showed no serious AEs and no increase in AEs with resmetirom alone or in combination with statins.

Conclusion: The resmetirom US label recommends resmetirom use with 98% of statin doses used by NASH patients; in addition, statin drug levels (PK) in Phase 3 patients on resmetirom were within the range of statin PK variability. NASH patients on statins had lower baseline liver enzymes than patients not on statins. Transient increase to approximately 1.3 times baseline at week 4, not generally above the level in patients not on statins, was observed in patients on resmetirom and statins; no significant week 4 elevations were observed in patients on resmetirom not on statins.
Liver enzymes improved relative to baseline over time in resmetirom-treated patients compared with placebo, independent of statin use.
No statin-related safety findings were noted in MAESTRO-NASH patients who took statins
Efficacy measures, including lipid lowering and NASH and fibrosis biopsy endpoints, were similar and statistically significantly improved in resmetirom-treated patients whether on statins or not on statins.

[31]

INDEPENDENT VALIDATION OF SECOND HARMONIC GENERATION/TWO PHOTON EXCITATION IMAGING AND ARTIFICIAL INTELLIGENCE-BASED SNOF INDEX FOR METABOLIC DYSFUNCTION ASSOCIATED STEATOHEPATITIS CIRRHOSIS ASSESSMENT

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Abstract Category: Therapeutic Trials - MASH/Liver Fibrosis – Humans

Background Information/Purpose –The Septa-Nodule-Fibrosis index (SNOF) was developed from a cohort of Metabolic dysfunction-Associated Steatohepatitis (MASH) cirrhosis with portal hypertension (PH) using machine learning (Noureddin et al. Aliment Pharmacol Ther 2023; 57: 409-2017). This novel index quantifies cirrhosis characteristics by features like septa width, length, cellularity; cirrhotic nodule diameter, area, number; and fibrosis parameters like number, length, perimeter, width of fibres. Initially, SNOF index demonstrated predictive value for clinical outcomes relevant to MASH cirrhosis, like hepatic venous pressure gradient (HVPG), clinically significant PH (CSPH), and varices. This study aims to validate SNOF on an independent cirrhotic cohort with pathologist-based staging to establish its use across different MASH cirrhosis populations and its relationship with histopathological staging.

Methods- We analyzed 598 unstained liver biopsies from BMS Falcon 1 & 2 trials (NCT03486899, NCT03486912) having patients with early & advanced cirrhosis (NASH-CRN F3 & F4, respectively). Spearman correlation (r-values) was used for correlations between SNOF and NASH-CRN staging & Ishak staging. We also compared changes in SNOF (ΔSNOF value; change in SNOF from Baseline to End-of-treatment) for pathologist-based progression (≥1-stage fibrosis increase), no-change (unchanged fibrosis stage), and regression (≥1-stage fibrosis decrease) biopsies of patients by Ishak & NASH-CRN systems.

Results- Study population had mean age of 58.06 years (median age 60 years); 40.3% were male, 59.7% female. Of the biopsies, 55.9% were F3, and 39.3% were F4 (NASH-CRN fibrosis staging). Median NAS scores were 1 for steatosis, 2 for ballooning, and 3 for lobular inflammation. Box-whisker plots show stage-wise correlation cut-offs, indicating strong correlation values for SNOF with both NASH-CRN (r = 0.604) and Ishak staging (r = 0.65) for fibrosis. SNOF increased in progression patients for both Ishak and NASH-CRN and decreased in both no-change and regression patients, with greater decrease in regression cohort; for both NASH-CRN and Ishak staging.

Conclusion- SNOF has significant correlation with both NASH-CRN and Ishak fibrosis staging and their longitudinal changes, useful as a comprehensive tool to quantify cirrhosis features in patients with MASH cirrhosis in clinical trials and clinical practice. SNOF, as a quantifiable measure of cirrhosis severity, can help predict treatment outcomes in drug trials. Future research should validate it in larger, diverse cohorts, explore its predictive capabilities in longitudinal studies and integrate it into clinical practice to enhance patient management. Additionally, linking SNOF to clinical outcomes, predicting treatment response from initial biopsies, and identifying cirrhosis from other causes like congestive hepatopathy can be crucial areas of focus.

[32]

COMPARATIVE EVALUATION OF ZONAL FIBROSIS PATTERNS IN PEDIATRIC AND ADULT METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS BIOPSIES USING SECOND HARMONIC GENERATION/TWO PHOTON EXCITATION-BASED QFIBROSIS ANALYSIS

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Abstract Category: Pathogenesis, Translational Science, NAFLD/MASH, Liver Fibrosis, Humans

Background Information/Purpose –Metabolic dysfunction-associated steatotic liver disease (MASLD) is prevalent among children, constituting the most common chronic liver ailment. Prior studies of liver biopsies from pre-adolescent children with metabolic dysfunction-associated steatohepatitis (MASH) identified an alternate pattern characterized by zone 1 centered steatosis, inflammation, and fibrosis, usually without ballooning, which may progress to advanced fibrosis. The aim of this study was to evaluate pediatric MASH biopsies using Second Harmonic Generation (SHG)/Two-Photon Excitation (TPE) microscopy and Artificial Intelligence (AI) analysis and compare the fibrosis patterns and distribution with biopsies from adults with MASH.

Methods: Nine unstained biopsies from children (aged 8 to 16 years) with MASH underwent SHG/TPE and AI analysis, yielding qFibrosis continuous values categorized into qFibrosis stages, based on pre-defined cut-offs. Biopsies were segregated into early (qF0/qF1/qF2; n=3) and advanced (qF3/qF4; n=6) fibrosis groups. Comparative analysis involved an adult cohort from a MASH clinical trial (NCT02855164), similarly categorized into early (n=96) and advanced (n=60) fibrosis stages. Fibrosis distribution in both cohorts was plotted on radar maps illustrating portal; periportal; perisinusoidal (zone 2), pericentral and central vein fibrosis, with zonal differences statistically significant at $p \leq 0.05$ by Spearman test.

Results: In the early fibrosis groups, pediatric biopsies exhibited significantly greater perisinusoidal (PS) (p=0.03) and more portal fibrosis compared to adults. In advanced fibrosis groups, pediatric biopsies demonstrated significantly less portal fibrosis (p=0.02) along with markedly increased PS fibrosis (p=0.01) compared to adult biopsies. Additionally, pediatric biopsies in advanced fibrosis group had more fibrosis in periportal (PP) and pericentral (PC) regions compared to adult biopsies.

Conclusions: This quantitative digital evaluation of MASH fibrosis highlights significant differences in zonal fibrosis distribution in pediatric MASH biopsies compared to adults. During the early fibrosis stage, pediatric biopsies show increased perisinusoidal and portal fibrosis in contrast to their adult counterparts. At advanced stages, there is significantly less portal fibrosis in pediatric biopsies compared to adults, although perisinusoidal fibrosis remains significantly greater in the pediatric group. The observed differences in fibrosis patterns hold potential implications for accurate assessment of fibrosis regression in pediatric MASH clinical trials.

[33]
MASH IS THE ONLY ETIOLOGY OF CIRRHOSIS WITH AN INCREASING INCIDENCE

Daniel Huang

Abstract Category: Clinical Epidemiology – MASH/Liver Fibrosis

Background Information/Purpose –The burden of cirrhosis and other chronic liver diseases has changed in recent years due to shifts in the contributing etiologies. We estimated the burden of cirrhosis and other chronic liver diseases, including etiological and regional differences, across 204 countries and territories from 2010 to 2021.

Approach and Results: We analyzed temporal trends in the burden of cirrhosis and other chronic liver diseases utilizing data from the 2021 Global Burden of Disease study. We estimated annual frequencies and age-standardized rates (ASR) of incident cases, deaths, and disability-adjusted life-years (DALYs) by sex, country, World Health Organization region, and its contributing etiologies. In 2021, there were an estimated 58,417,006 incident cases, 1,425,142 deaths, and 46,417,777 DALYs related to cirrhosis and other chronic liver diseases. From 2010 to 2021, there was a rise in age-standardized incidence rates (ASIRs) (APC: +0.35%) but age-standardized death rates (ASDRs) (APC: -1.74%) and age-standardized disability-adjusted life-years (ASDALYs) (APC: -1.85%) declined. Cirrhosis related to metabolic dysfunction associated steatohepatitis (MASH) contributed to 48,310,981 incident cases in 2021 and was largely responsible for the overall increase in ASIRs from 2010 to 2021. Cirrhosis and other chronic liver diseases related to MASH was the only etiology with a rise in ASIR (APC: +0.86%). Age-standardized deaths related to all etiologies of cirrhosis and other chronic liver diseases declined during the study period. Age-standardized deaths and DALYs related to MASH increased in the Americas, unlike all other world regions where they declined or remained stable.

Conclusions: Age-adjusted deaths related to cirrhosis and other chronic liver diseases are declining. However, the age-adjusted incidence of cirrhosis and other chronic liver diseases is increasing, driven by increases in the incidence of MASH.

[34]
STAIN-FREE DIGITAL PATHOLOGY IMAGING REVEALS MICROARCHITECTURAL INSIGHTS INTO DISEASE ACTIVITY AND SCAR EVOLUTION TO ENABLE OUTCOME PREDICTION IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Abstract Category: Pathogenesis, Translational Science, NAFLD/MASH, Liver Fibrosis, Humans

Background Information/Purpose –Digital quantification of scarring from either stained or stain-free liver sections reduces observer-related variability in the histological assessment of metabolic dysfunction-associated steatotic liver disease (MASLD). To date, computational methods have mainly provided ordinal scores analogous to those provided by a pathologist as disease outcomes are strongly correlated with stage. Using SteatoSITE, an integrated-multimodal data commons for MASLD research, we applied stain-free imaging to develop tools for outcome prediction based on architectural features imperceptible to human observers.

Method: Sections from n=452 biopsies were randomized into training (300) or test (152) sets and imaged using second harmonic generation/two-photon excitation fluorescence (SHG/TPEF) microscopy. 5 of 184 fibrosis parameters have previously been used to derive separate fibrosis-based indices for risk of clinical outcome mortality (COMI-F) and clinical outcome decompensation (CODI-F). By feature traversing, the effect of adding 65 steatosis and 21 ballooning parameters to COMI and CODI was tested, and improved composite outcome indices (-FS and -FB) generated. In the testing set, the predictive power of the new composite indices was compared with assigned NASH-CRN fibrosis stage (F0/1/2 v F3/4), stain-free imaging derived qFibrosis stage (qF0/1/2 v qF3/4), and previously derived fibrosis-only indices using Kaplan–Meier analysis and Cox proportional hazards modelling.

Results: Composite indices incorporating ballooning parameters (COMI-FB and CODI-FB) demonstrated superior predictive power for all-cause mortality and hepatic decompensation, respectively, compared to COMI-F, CODI-F, qFibrosis stage, and NASH-CRN fibrosis scores. Similarly, composite indices for all-cause mortality (COMI-FS) and hepatic decompensation (CODI-FS) generated by including steatosis parameters also had greater predictive power than the COMI-F, as well as qFibrosis-derived stage and NASH-CRN fibrosis score.

Conclusion: SHG/TPEF imaging-derived microarchitectural features of scarring and disease activity improve predictive value for all-cause mortality and liver-related events beyond traditional fibrosis-based scores or ordinal staging. These indices may offer enhanced participant stratification and endpoint analysis for clinical trials. Prospective validation is essential to establish the relationship between baseline microarchitectural features, their modification following treatment, and associated clinical outcomes.

Table: Hazard ratios and p-values for prediction of all-cause mortality and hepatic compensation using composite stain-free fibrosis, ballooning and steatosis parameter-derived indices compared with NASH-CRN fibrosis scores, qFibrosis scores, and stain-free fibrosis parameter-only indices.

	All-cause mortality (MI)			Hepatic decompensation (DI)		
	Hazard ratio (HR)	*p*-value	95% HR confidence intervals	Hazard ratio	*p*-value	95% HR confidence intervals
NASH-CRN fibrosis (F0/1/2 v F3/4)	3.41	0.003	1.428-8.15	3.65	<0.001	1.814-7.353
qFibrosis (qF0/1/2 v qF3/4)	3.07	0.007	1.295-7.257	3.59	<0.001	1.295-7.257
Fibrosis parameter-only indices COMI-F & CODI-F (low v high risk)	4.49	0.003	1.5-13.38	5.96	<0.001	2.924-12.14
Composite ballooning and fibrosis parameter indices COMI-FB & CODI-FB (low v high risk)	**7.84**	**<0.001**	**1.824-33.72**	**5.98**	**<0.001**	**2.944-12.14**
Composite steatosis and fibrosis parameter indices COMI-FS & CODI-FS (low v high risk)	**5.00**	**<0.001**	**1.681-14.88**	**5.87**	**<0.001**	**2.895-11.92**

[35]
DENIFANSTAT SHOWED ANTIFIBROTIC EFFECT BOTH ON CONVENTIONAL AND DIGITAL PATHOLOGY IN A METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASH) PHASE 2B TRIAL (FASCINATE-2)

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Abstract Category: Therapeutic Trials - MASH/Liver Fibrosis – Humans

Background: Denifanstat (DENI), a fatty acid synthase inhibitor in development for MASH, met statistical significance in histology endpoints in the phase 2b FASCINATE-2 trial. Digital pathology complements conventional pathology by providing more sensitive and quantitative analysis of histologic changes. We aimed to describe the fibrosis response to DENI using both conventional pathology and qFibrosis features.

Method: FASCINATE-2 (NCT04906421) randomized 168 patients with biopsy-proven MASH, NAS ≥ 4, and NASH-CRN fibrosis stage 2 or 3, to receive either oral once-daily DENI 50 mg or placebo (PBO) (2:1) for 52 weeks. An unstained slide was evaluated by second harmonic generation/two-photon excitation digital pathology incorporating steatosis correction for qFibrosis.

Results: At week 52, NASH-CRN scores showed DENI led to fibrosis improvement by at least 1 stage without worsening of MASH in 40.7% vs 17.8% in PBO (p=0.0051). Evaluation of at-risk subgroups using this same endpoint showed (DENI vs PBO):
-F3 fibrosis: 49% vs 13%, p=0.0016; and 34% vs 4 %, p=0.0065 for at least 2 stage improvement without worsening of MASH
-With concomitant GLP1-RA use: 42% vs 0%, p=0.034
-In patients with type 2 diabetes: 40% vs 19%, p=0.038
-In PNPLA3 I148M carriers: 30% vs 6% placebo, p=0.022
The proportion of patients progressing to cirrhosis was significantly lower in DENI (5%) vs PBO (11%, p=0.0386). Continuous qFibrosis was significantly decreased in DENI (-1.0) vs PBO (-0.1, p<0.0001). In patients with F3 fibrosis, continuous qFibrosis was significantly decreased in DENI (-1.3) vs PBO (-0.2, p<0.001). Digital morphometric analysis in patients with F3 showed a significant reduction of fibrosis features in DENI vs an increase in the PBO group:
-Septa Area: -21,601 vs 12,260 μm^2, p=0.0155
-Septa Length: -148 vs 109 μm, p=0.0016
-Septa Width: -16 vs 7 μm, p=0.0464
In the subgroup of patients classified as "no change" in fibrosis by conventional pathology, continuous qFibrosis demonstrated a significant decrease (-0.9) in those treated with DENI vs PBO (-0.1; p<0.0001).

Conclusion: DENI showed statistically significant antifibrotic effects on both conventional and digital pathology, including in difficult-to-treat MASH populations. Digital pathology also identified DENI fibrosis improvement compared to PBO in those classified as "no change" by conventional pathology, suggesting that longer treatment duration with DENI may potentially increase the proportion of responders.

[36]
CAUSES OF DEATH, MORTALITY RATES, AND THE ROLE OF SOCIO-DEMOGRAPHIC RISK FACTORS AND BIOMARKERS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS MORTALITY IN MORE THAN 18,000 REAL WORLD PATIENTS FROM THE UNITED STATES

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Abstract Category: Clinical Epidemiology – MASH/Liver Fibrosis

Background: Previous real-world studies of mortality risks in patients with metabolic dysfunction-associated steatohepatitis (MASH) were limited by sample size, time of data collection, being single center, biopsy based, or having a broad focus on steatotic liver disease. This study investigates mortality rates, causes of death, and the role of socio-demographic risk factors and biomarkers that could be associated with mortality in a large real-world MASH population.

Method: US Optum Market Clarity linked claims and electronic health records from 2016–2021 were used to identify patients with MASH, defined by the first recorded ICD10 diagnosis code (K75.81 Nonalcoholic steatohepatitis) and presence of AST, ALT, and platelets tests carried out within 3 months of the index date. Patients with cancer, bariatric surgery, type 1 diabetes, and other chronic liver diseases were excluded. Risk factors included age, sex, race, region, comorbidities, FIB-4 fibrosis score, and routinely collected biomarkers such as LDL cholesterol, triglycerides, eGFR, and HbA1c. Associations between risk factors and mortality was estimated in survival models. In a stratified sub-population analysis, crude mortality incidence rates were calculated in MASH patients with body mass index (BMI) ≥25 and type 2 diabetes (T2D) vs patients with BMI ≥25 without any liver diseases and T2D.

Results: 18,710 MASH patients (mean age 44 years, 54% female, 80% White, 95% with BMI ≥25, 52% with T2D) had 6.5 years of follow-up after diagnosis: 1465 patients died (70% from cardiovascular disease and 17% from liver-related causes). African Americans (vs White) and South residents (vs North-East) had higher all-cause mortality rates (hazard ratios [HRs] of 1.33 and 1.46, respectively). A decrease in eGFR of 10 mL/min/1.73m² and having ≥3 comorbidities (vs none) were also associated with increased mortality (HRs of 1.12 and 1.56, respectively). The mortality incidence rate was 31 per 1000 persons-year (py) in MASH with BMI ≥25 and T2D (5 times higher than those with BMI ≥25 without liver diseases/diabetes) and 25 per 1000 py in the overall MASH cohort.

Conclusion: Mortality incidence rates are especially high in MASH patients who are overweight/obese and have T2D. Higher mortality in African Americans and South residents suggest socio-demographic differences; this may be due to less access to health care. Also, the eGFR-mortality association signaled that kidney disease prevention is important.

Originally presented at International Liver Congress 2024, organized by the European Association for the Study of the Liver (EASL)

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Data sharing statement
To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to clinical study data pertinent to the development of the publication. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data when it becomes available on Vivli - Center for Global Clinical Research Data, and earliest after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete and other criteria are met. Please visit Medical & Clinical Trials | Clinical Research | MyStudyWindow for further information.

[37]
EARLY EXPERIENCE WITH RESMETIROM TO TREAT METABOLIC DYSFUNCTION ASSOCIATED STEATOHEPATITIS WITH FIBROSIS IN A REAL-WORLD SETTING

Naga Chalasani, MD

Abstract Category: Disease Management of MASH/Liver Fibrosis Patients (including comorbidities)

Abstract
Resmetirom, a novel THRβ agonist was conditionally approved recently in the United States for treating MASH with stage2 and 3 fibrosis. However, its availability to patients requires preauthorization by the payors and is dispensed only through selected specialty pharmacies. We established a multistakeholder and multistep resmetirom prescription process pivoting to a dedicated pharmacist. It incorporates liver biochemistry testing at 12 weeks and liver clinic follow-up at 6 months after starting resmetirom. Fifteen hepatology providers prescribed resmetirom to 113 patients from 4/1/24 to 11/8/24, with histologic eligibility in 70% and non-invasive criteria in 30%. Resmetirom treatment was approved for 110 patients (97%), including 8 patients receiving the pharmaceutical company's patient assistance and 6 patients receiving bridge support to cover the co-pay. Eighty-three patients initiated resmetirom at an average 30 days after its prescription.Adverse events (AE) were reported by 41% of patients taking resmetirom and they were predominantly related to gastrointestinal symptoms and pruritus and/or rash with no evidence for hypersensitivity. Thirteen patients (16%) discontinued resmetirom after an average of 25.5 days (range 2-68 days), with 11 patients discontinuing due to AEs. The AEs leading to discontinuation were nausea, diarrhea and vomiting in 4, right upper quadrant discomfort in 2, left lower quadrant pain in 1, rash with pruritus in 1, pruritus and rash with indirect hyperbilirubinemia in 1, dizziness in 1 and mental fogginess in 1 patient. Follow-up liver biochemistries available in 24 patients showed no evidence for drug-induced liver injury. In summary, we established a prescribing process which effectively dispensed resmetirom to almost all patients who were prescribed resmetirom. One in six patients discontinued resmetirom, primarily due to side effects. This high discontinuation rate may be mitigated by modifying our follow-up approach from "prescribe and forget" to "prescribe and closely follow".
Key words: MASH, Resmetirom, VCTE, LSM, Fibrosis, DILI, Adverse events

[38]

Availability, Cost, and Utilization of Magnetic Resonance Elastography

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Abstract Category: Disease Management of MASH/Liver Fibrosis Patients (including comorbidities)

Background Information/Purpose –Magnetic Resonance Elastography (MRE) has emerged as a highly accurate diagnostic tool for staging liver fibrosis, particularly in technically challenging populations like metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH). While the diagnostic performance of MRE in this application is now well recognized, practice guidance often characterizes MRE as having limited availability and high cost. The goal of this study was to provide an updated assessment of the availability, cost, and utilization of MRE in the U.S.

Methods- Data on MRE installations were compiled from leading MRI manufacturers, and reimbursement rates were sourced from Centers for Medicare & Medicaid Services (CMS). Data on VCTE locations in the US were obtained from the manufacturer's website. Utilization trends were analyzed using historical CMS data from 2019–2022.

Results- The U.S. currently has approximately 1,300 MRE installations, compared to roughly 1,600 Fibroscan devices. Among Fibroscan installations, the availability of XL probes required for high-BMI patients is unknown, likely reducing the number of units available for MASH fibrosis assessment. MRE utilization grew by 20% in 2022 according to CMS data, compared to 3% for Fibroscan. In total, there has been an 87% increase in MRE scans since 2019 (compared to 18% for VCTE since 2019). Notably, this does not include MRE exams added to a full abdominal MRI exam, which would not be included in the CMS utilization totals. In cost analysis, the average VCTE procedure cost (CPT code 76981) was $104 compared to $203 for MRE (CPT code 76391). However, the final patient expense is often higher due to office/consultation fees (E/M charges of an additional $91-$220 depending on complexity).

Conclusion-MRE and VCTE have similar availability in the U.S., with sufficient installations to characterize both as "widely available." MRE incurs similar total costs as VCTE for moderate complexity cases and is less expensive for high complexity cases. Perhaps due to this dynamic, MRE utilization has grown four times that of VCTE since 2019. Given the superior diagnostic performance of MRE, especially in high-BMI patients, accurate awareness of the favorable cost and availability profile in the US will be helpful in decisions for optimum patient management.

Figure 1.
CMS Claims Data, VCTE and MRE, 2019-2022

	2019	**2020**	**2021**	**2022**	**Growth since 2019**
VCTE (number	51229	45053	58430	60266	
Annual growth		-12.10%	29.70%	3.10%	18%
	2019	**2020**	**2021**	**2022**	
MRE (number	2508	2831	3887	4680	
Annual growth		13%	37%	20%	87%

Figure 2.
CMS Procedure Cost Data, 2024

	VCTE procedure	E/M low complexity	E/M moderate	E/M high complexity
Facility	$104	$112	$167	$220
	Total:	**$216**	**$271**	**$324**
Non-facility	$104	$91	$128	$180
	Total:	**$195**	**$232**	**$284**
	MRE			
Facility	Total			**$289**
Non-facility	Total			**$206**

*shaded = common E/M for MASLD/MASH patients

[39]

ANALYSIS OF NON-INVASIVE LIVER BIOMARKERS IN A PHASE 2 TRIAL OF THE GLUCAGON AND GLP-1 RECEPTOR DUAL AGONIST SURVODUTIDE IN PEOPLE WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) AND FIBROSIS

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Abstract Category: Therapeutic Trials - MASH/Liver Fibrosis – Humans

Background: We evaluated non-invasive liver biomarkers from a phase 2 trial of survodutide, a novel glucagon receptor/glucagon-like peptide-1 receptor dual agonist for the treatment of metabolic dysfunction-associated steatohepatitis (MASH) and fibrosis.

Methods: In this multinational, double-blind, phase 2 trial (NCT04771273), 295 people aged 18–80 years with biopsy-proven MASH (Non-alcoholic fatty liver disease Activity Score ≥4), liver fibrosis (stage F1–F3) and body mass index ≥25 kg/m^2 were randomized to once-weekly subcutaneous injections of placebo (PBO) or survodutide 2.4, 4.8 or 6.0 mg (escalated over up to 24 weeks). In this analysis, we evaluated percentage of participants with >30%, >50% and >70% reduction in liver fat content (LFC; magnetic resonance imaging proton density fat fraction [MRI-PDFF] assessed; paired MRI data), resolution of steatosis (LFC <5%; MRI-PDFF assessed) with or without >17 U/L reduction in alanine transaminase (ALT; paired MRI data), absolute change in enhanced liver fibrosis (ELF™) score, relative change in propeptide of type III collagen (PRO-C3), and absolute and relative change in liver stiffness (transient elastography [VCTE; FibroScan] assessed) from baseline (BL) to Week 48. These biomarkers were analyzed according to the actual dose received at the start of the maintenance period.

Results: The number of participants with significant >30%, >50% and >70% reduction in LFC (MRI-PDFF) was met in up to 87.0%, 78.2% and 52.7% with survodutide vs 19.7%, 3.0% and 0.0% for PBO, respectively. LFC <5% with an ALT reduction of >17 U/L was met in up to 45.7% vs 0.0% and without ALT reduction in up to 54.3% vs 0.0% with survodutide vs PBO, respectively. Absolute change in ELF score was up to –0.619 with survodutide vs –0.003 with PBO; relative change in PRO-C3 was up to –26.32% vs 5.47%, respectively. The absolute (relative) change in liver stiffness (VCTE) was up to –5.09 kPa (–32.99%) with survodutide vs –1.18 kPa (3.44%) with PBO, respectively.

Conclusion: Participants that received survodutide had significant improvements in LFC (MRI-PDFF assessed), liver stiffness (VCTE assessed), liver enzymes and other markers of fibrosis (ELF, PRO-C3) which was correlated with improvements in histological endpoints.

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[41]
USE OF THE LIVERRISK SCORE FOR PREDICTION OF FIBROSIS AND ALL-CAUSE MORTALITY RISK IN UNITED STATES ADULTS

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Abstract Category: Diagnostic Procedures - MASH/Liver Fibrosis

Background Information/Purpose –Despite the growing morbidity and mortality of metabolic dysfunction-associated steatotic liver disease, efficient screening is lacking. FIB-4, a non-invasive test (NIT) recommended for initial screening, has higher false negative rates in at-risk groups vs. the general population, for identifying significant fibrosis (as measured by LSM from VCTE). The LiverRisk Score (LRS), based on blood-tests and demographics, was developed for prediction of liver fibrosis and liver-related outcomes in the general population. This study evaluated (1) the performance of LRS for prediction of LSM ≥8 kPa compared to FIB-4 and (2) the association of LRS-defined risk groups with mortality.

Methods- An observational analysis was conducted of data from the NHANES 2017-2020 cycle, including participants with complete information to calculate the LRS (i.e., age, sex, AST, ALT, GGT, fasting glucose [imputed from non-fasting when missing], total cholesterol, and platelet count). Performance of LRS vs. FIB-4 for prediction of LSM ≥8 kPa was estimated as area under the curve (AUC) by survey-weighted logistic regression of LSM ≥8 kPa vs. the LRS or FIB-4. Discrimination was further assessed in at-risk subgroups. Association of LRS risk groups (6 to <8, 8 to <15, and ≥15) with all-cause mortality was evaluated in participants from NHANES III (1988-1994) and continuous NHANES cycles from 1999-2016, linked to National Death Index (NDI) data through 2019, with survey-weighted Cox proportional-hazards models adjusting for self-reported age, sex, and race/ethnicity.

Results- The unweighted study population included N=7,005 participants for prediction of LSM ≥8 kPa, and N=57,101 for prediction of all-cause mortality (median follow-up: 12.3 years). The LRS demonstrated superior discrimination of LSM ≥8 kPa in all adults, with AUC (95% CI) of 0.73 (0.71-0.75) vs. 0.63 (0.61-0.65) for FIB-4. For fixed sensitivity at 90%, LRS had higher specificity vs. FIB-4 (33% vs. 17%). Compared to LRS <6, higher LRS scores were associated with higher all-cause mortality, with adjusted hazard ratios (95% CI) of 1.67 (1.57-1.78) for LRS 6 to <8, 2.61 (2.33-2.92) for 8 to <15, and 4.81 (3.69-6.27) for ≥15.

Conclusion- In US adults, the LRS demonstrated superior discrimination vs. FIB-4 for prediction of LSM ≥ 8kPa, which could facilitate initial screening. Notably higher all-cause mortality risk was observed for LRS ≥ 6, emphasizing its clinical utility.

THANK YOU FOR ATTENDING!

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