

models such as the Model for End Stage Liver Disease (MELD) or intensive care prognostic schema accurately predict hospital mortality. Multivariate methods applied to nuclear magnetic resonance (NMR) spectroscopy of serum have demonstrated correlation with MELD score but whether metabolic profiling predicts outcome in these patients is unknown.

Methods 80 patients referred to Kings College Hospital with decompensated cirrhosis were studied with 20 healthy controls. Plasma was drawn on admission for subsequent ^1H NMR spectroscopy using a Carr-Purcell-Meiboom-Gill sequence in a 600 MHz Bruker Avance spectrometer. Full resolution NMR spectra were used in an orthogonal projection to latent structures discriminant analysis (OPLS-DA) to predict hospital mortality.

Results Patients had a median (range) age of 55 (23–75) years with 51 (64%) male. Aetiology of cirrhosis was alcohol related in 40 (50%), autoimmune in 15, viral hepatitis in 10, non-alcoholic steatohepatitis (NASH) in 5, with haemochromatosis and cryptogenic cirrhosis the causes in the remainder. Median (range) MELD score was 14 (6–40) with 18 patients not surviving to hospital discharge. The OPLS-DA model accurately discriminated between patients and healthy controls ($R_2(X) = 0.65$, $R_2(Y) = 0.84$, $Q_2(Y) = 0.76$, cross-validated (leave-one out) sensitivity and specificity 100%, CV-ANOVA $p = 10^{-27}$). Metabolites increased in patients were lactate, tyrosine, and glucose with LDL, VLDL and phosphocholines being increased in controls. OPLS-DA accurately discriminated between survivors and non-survivors ($R_2(X) = 0.63$, $R_2(Y) = 0.64$, $Q_2(Y) = 0.37$, sensitivity 100%, specificity 95% CV ANOVA $p = 10^{-6}$). Metabolites increased in non-survivors included lactate, tyrosine and phenylalanine with lipid and phosphocholine resonances reduced in non-survivors. Removing 1/3 of patients at random from the learning set, remodelling and predicting outcome for these patients resulted in an AUROC of 0.95 (95% CI 0.87 to 1.00, sensitivity 93%, specificity 86%) for predicting survival using NMR profiling in comparison with 0.78 for MELD ($p < 0.001$).

Conclusion Plasma metabolic profiling with ^1H NMR spectroscopy in patients with cirrhosis and acute-on-chronic liver failure can accurately describe a metabolic phenotype of non-surviving patients. Validation of these techniques in larger datasets is required.

Competing interests M McPhail: Grant/Research Support from: Wellcome Trust, UK, D Shawcross: None Declared, I Coltart: None declared, E Want: None declared, K Veselkov: None declared, M Crosse: None declared, C Willars: None declared, G Auzinger: None declared, J O'Grady: None declared, W Bernal: None declared, E Holmes: None declared, J Wendon: None declared, S Taylor-Robinson: None declared.

PTU-047 THE CLINICAL UTILITY AND COST-EFFECTIVENESS OF NON-INVASIVE TESTS FOR DETECTING FIBROSIS IN PATIENTS WITH SUSPECTED ALCOHOL-RELATED LIVER DISEASE

doi:10.1136/gutjnl-2012-302514c.47

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Introduction The use of non-invasive liver tests (NILTs) for assessing hepatic fibrosis carries fewer risks than liver biopsy. However, their clinical utility and cost-effectiveness, in patients with suspected alcohol-related liver disease, are unknown. This study explored whether the Enhanced Liver Fibrosis (ELF) test, FibroTest, and FibroScan are likely to be cost-effective in a UK setting.

Methods Systematic reviews of the clinical effectiveness of the three NILTs under study and of the morbidity/mortality associated with

liver biopsy were undertaken and used, where possible, to populate a mathematical model constructed to simulate the experience of patients suspected of having alcohol-related liver injury. The model used the following strategies: (1) biopsy all; (2) use a NILT for triage and biopsy more selectively; and (3) use a NILT alone to determine diagnosis and subsequent management. Thirty-six separate scenarios were evaluated varying the type and sensitivity of the liver biopsy, the accuracy of the non-invasive tests, and the disutility associated with the biopsy procedure.

Results No clear conclusions could be drawn, following the systematic reviews, about the accuracy of these three NILTs in the diagnosis of alcohol-related liver disease because there was significant heterogeneity in the published studies, particularly in relation to drinking behaviour and diagnostic cut-offs. The assessment was also confounded by the paucity/absence of data on: (1) the sensitivity of the liver biopsy; and (2) the difference in costs and health between abstinent patients and those who continued to drink. There was wide variation in the threshold level for a decrease in abstinence rates using NILTs in both triage and replacement strategies. The maximum threshold value was 6.1 percentage points with the minimum value being zero percentage points. There was also wide variation in the threshold levels for the incidental gains associated with biopsy using NILTs in both triage and replacement strategies. The maximum value was 0.188 QALYs with the minimum value being zero QALYs.

Conclusion The clinical utility and cost-effectiveness of these three NILTs cannot be assessed, at the present time, primarily because information on the key variables needed to populate the model are lacking. Thus, caution should be exercised in their use, in patients with suspected alcohol-related liver disease, at the present time.

Competing interests None declared.

PTU-048 RIFAXIMIN FOR THE TREATMENT OF HEPATIC ENCEPHALOPATHY; A META-ANALYSIS OF RANDOMISED STUDIES

doi:10.1136/gutjnl-2012-302514c.48

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Introduction The non-absorbable antibiotic rifaximin has been used to treat hepatic encephalopathy (HE) since the 1980s. Interest in its use increased following a recent Phase III study showing that treatment with rifaximin over 6-months resulted in a relative reduction in the risk of breakthrough HE of 58% compared to placebo (Bass *et al*, 2010). The aim of this study was to evaluate the efficacy and safety of rifaximin for the treatment of all types of HE in patients with cirrhosis against a variety of comparative regimens.

Methods A language unrestricted search for papers published between January 1983 and September 2011 was undertaken utilising 11 databases. All HE treatment trials were scrutinised and randomised trials identified. Raw data were obtained from six trials. Data were extracted on (1) the numbers of patients showing improvement overall; (2) the means ($\pm 1\text{SD}$) for mental state, asterixis, number connection tests (NCT), EEG and blood ammonia; and (3) adverse events. Fixed effect model meta-analyses were applied, subdivided by population type. Random effects analyses were used when statistically significant heterogeneity of results occurred. Overall relative proportions were calculated for binary outcomes and standardised mean differences (SMD) for quantitative outcomes.

Results 17 trials were identified comparing rifaximin to non-absorbable disaccharides (9 trials), other antibiotics (6 trials) or "no

treatment" (2 trials) in patients with either "acute" (4 trials), "chronic" (8 trials), or "minimal" (3 trials) HE or else for the "prevention of HE recurrence" (2 trials). Most trials were of adequate quality; the total sample size was 1037 patients, but data were not extractable for all outcomes. The relative proportion of patients experiencing clinical improvement with rifaximin, compared to all control regimen, was 1.26 (95% CI 1.05 to 1.52, $p=0.014$). Broadly consistent benefits were shown for individual outcome variables for example, asterixis (SMD -0.32 , 95% CI -0.62 to -0.02 , $p=0.038$, 5 trials); EEG (SMD -0.49 , 95% CI -0.92 to -0.07 , $p=0.023$, 2 trials) and blood ammonia (SMD -0.25 , 95% CI -0.48 to -0.02 , $p=0.034$, 8 trials), although not for mental status (SMD -0.19 , 95% CI -0.47 to 0.10 , $p=0.20$, 5 trials) or NCTs (SMD 0.05 , 95% CI -0.19 to 0.28 , $p=0.8$, 7 trials). SMDs were stronger in the eight trials in chronic hepatic encephalopathy (asterixis -0.34 ; EEG -0.56 ; blood ammonia -0.26 ; mental state -0.45 ; NCTs 0.36). No significant differences were observed in side-effects between rifaximin and control regimens.

Conclusion Rifaximin is an efficacious and safe treatment for HE when compared to a variety of other treatments regimens; the benefits are most marked in patients with chronic HE.

Competing interests None declared.

PTU-049 MODULATION OF TOLL-LIKE RECEPTOR GENES WITH SELECTIVE GUT DECONTAMINATION IN CIRRHOTIC ANIMALS PREVENTS THE DEVELOPMENT OF ACUTE-ON-CHRONIC LIVER FAILURE (ACLF)

doi:10.1136/gutjnl-2012-302514c.49

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Introduction Acute deterioration in the liver function following precipitating illness in patients with cirrhosis often lead to multiple organ failure. Inflammation is thought to be a major contributing factor. We hypothesised that toll like receptor's (TLRs) play a pivotal role in lipopolysaccharide (LPS) mediated cytokine surge in patients with cirrhosis culminating in acute-on-chronic liver failure (ACLF). Selective gut decontamination with Norfloxacin would dampen this inflammatory cascade.

Methods Global hepatic gene expression was studied in a rodent model of cirrhosis induced by bile duct ligation (BDL) (Agilent microarray) and compared the results to sham animals. TLR related genes were among the differentially expressed genes in the liver. We validated gene expression in the Liver and Kidney in a second set of experiment in Sham, BDL, BDL+LPS, BDL+Norfloxacin, BDL+Norfloxacin+LPS groups using the quantitative real-time PCR. Cytokines (Becton Dickenson) and biochemistry were measured (COBAS Integra 400).

Results Among the several genes with high expression in the BDL group as detected by the microarray, both TLR 4 and 2 had significantly higher expression in liver and Kidney compared with the sham group. We also found a marked upregulation of the C-C motif ligand 2 (CCl2) and C-X-C motif ligand 2 (CxCl2) Furthermore, LPS administration in BDL animals accentuated not only the TLRs (4 and 2) expression in both kidney and liver but also the Cxcl2 and CCl2 in both these organs associated with deterioration organ function as suggested with a rise in the liver enzyme, creatinine and a rise in plasma and tissue cytokines. Norfloxacin pre-treatment in BDL group (BDL+Norfloxacin) attenuated the TLR4 and TLR2 expression in both liver and kidney. Selective decontamination with Norfloxacin in BDL +LPS animals limited the upregulation of TLR4 and TLR2 in the Liver and Kidney. It also prevented the upregulation of the Cxcl2 and CCl2 in both these organs. This was associated

with significant improvement in liver enzymes, creatinine and cytokines.

Conclusion This study shows that the liver and kidneys in cirrhotic animals are primed by upregulation of TLR's and its downstream inflammatory mediators in the Liver and Kidney which make them exquisitely sensitive to the effects of superimposed infection/inflammation leading to organ failure. Selective decontamination with Norfloxacin prevents the progression of ACLF by reducing gene expression of TLR 2 and 4 and its associated inflammatory adaptors.

Competing interests None declared.

PTU-050 EFFECT OF VITAMIN E AND ALFA LIPOIC ACID (ALA) IN NON-ALCOHOLIC FATTY LIVER DISEASE: A RANDOMISE PLACEBO CONTROL OPEN LABEL PROSPECTIVE CLINICAL TRIAL: V A I N TRIAL

doi:10.1136/gutjnl-2012-302514c.50

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Introduction Non-Alcoholic Fatty Liver Disease (NAFLD) is a global epidemic. NAFLD progress to Non-Alcoholic Steatohepatitis (NASH), cirrhosis and cancer. Obesity and insulin insensitivity is the hallmark. Liver participates in glucose and fatty acid homeostasis. Nonexpelled free fatty acid and its toxic metabolites impact oxidative stress; free radicals influx which initiate inflammatory cascade to Steatohepatitis (NASH) and activate fibrotic path causing cirrhosis. This clinical trial highlights the effects of anti-oxidants in NAFLD.

Methods One hundred and fifty-five (n=155) with BMI over 28% with NAFLD and NASH were recruited and randomised into Group A (n=35)- Control, Group B (n=40) ALA 300 mg, Group C (n=40) Vitamin E 700 IU and Group D (n=40) ALA plus Vitamin E orally for 6 months. Pre and Post BMI, HOMA, Triglyceride, Haemoglobin A1c, Alanine aminotransferase (ALT), Retinol Binding Protein 4, Tumour Necrosis factor α (TNF α), Leptin and adiponectin levels were compared. Everyone was allowed 1600 cal/day with modest exercise. Exclusion criteria: Diabetics, BMI >33%, Alcohol intake >30 g/day, Hepatitis B, C, Hypothyroidism, medications including herbs and supplements.

Results

% Changes	Group B (ALA)	Group C (Vit E)	Group D (ALA + Vit E)
δ Triglyceride	34.3%	37.5%	56.4%
δ HOMA	54.3%	53.7%	67.4%
δ ALT	20.8%	40.7%	44.8%
δ RBP4	46.2%	46.5%	61.9%
δ Leptin	44.8%	46.9%	58.6%
δ Adiponectin	55%	47.8%	52.6%
δ TNF- α	59.3%	61.9%	82.6%
δ Steatosis Score	75%	73.2%	78.7%
δ Fibrotic Score	5.9%	-6.7%	5.6%

Conclusion Pre and post analysis between ALA plus Vitamin E over placebo in 6 month; TG 43%, HbA1c 14%, HOMA 62.8%, ALT 14.4%, RBR4 50%, Leptin23%, Adiponectin19% TNF α 70%, and Steatotic score 70.7%. This clinical trial demonstrates the additive effects of ALA and vitamin E in NAFLD and NASH with significant improvements of inflammatory and steatotic score but no difference in the fibrotic score. Therapeutic application of ALA and Vitamin E should be considered for NAFLD.

Competing interests None declared.