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Strategies are needed to support people with alcohol use disorder and alcohol-related liver disease to take part in randomised clinical trials: results from the MIRAGE pilot trial of functional imagery training

Dhanda, A

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HNA1/HNA2 increases. However, the time at which the infused albumin (HMA) undergoes oxidative modification and changes in cognate circulating metabolites are not known. Our study aims to decipher the time dynamics of oxidized albumin and associated changes in the circulating metabolome in a rat model of ALD.

Method: ALD model was developed by feeding Lieber-DeCarli liquid diet (40% ethanol) to Long Evans rats for 28 weeks. Liver histology (ballooning, steatosis and neutrophil infiltration) and AST/ALT levels confirmed active ALD. HMA, *in-vitro* modified HNA1 and *in-vitro* modified HNA2 (2.5 g/kg) were injected intraperitoneally to the ALD rats (n = 3 each) at three time points: baseline, 24 hours and 48 hours. Plasma was collected at baseline, 5 minutes, 15 minutes, 30 minutes, 1 hour, 24 hours, 48 hours, 72 hours and post euthanasia. Oxidized albumin measurement and untargeted metabolomics was performed.

Results: At baseline (before injection), the ALD rats showed significant increase in HNA1 (42.61%) and HNA2 (24.99%). HMA infused ALD rats showed temporal increase in HMA levels (15%) (5 min to 72 hours) with a slight dip between 5 minutes and 1 hour. HNA1 levels decreased by 18% and there was no significant change in HNA2 levels. Untargeted metabolomics also showed temporal increase in histidine (anti-inflammatory), purine/pyrimidine, glutathione and pantothenate metabolism ($p < 0.05$) indicating the protective and anti-inflammatory activity of HMA. Interestingly, Infusion of HNA1 to ALD rats showed significant temporal increase (5 minutes to 72 hours) in HNA2 (10% to 32%) with simultaneous decrease in the HMA (10%) levels suggesting that HNA1 infusion increases the irreversible oxidation of HMA/HNA1 to HNA2. Metabolomics also showed temporal increase in spermidine synthesis (pro-inflammatory polyamines), ammonia recycling and phosphatidylcholine synthesis (pro-apoptotic phospholipids) ($p < 0.05$) documenting the pro-inflammatory and pro-apoptotic activity of HNA1. Unfortunately, HNA2 infused ALD rats died after 4 hours. We observed significant temporal increase of HNA2 (15%) (5 minutes to 4 hours) with significant and apparent decrease in HNA1 and HMA. Results of metabolomics analysis revealed an increase in fatty acid, amino-sugar, tryptophan, fructose, mannose and sphingolipid metabolism suggesting the increase of inflammatory metabolites in HNA2 infused ALD rats. The advanced oxidative state (AOS) of albumin was highest in HNA2 infused rats ($p < 0.05$).

Conclusion: Our results show that HMA infusion temporally decreases HNA1 levels with simultaneous increase in anti-inflammatory metabolites. HNA1/HNA2 infusion causes irreversible oxidation of albumin to HNA2 and increase in pro-inflammatory/pro-apoptotic metabolites in the circulation. Albumin modification time dynamics significantly correlate with their cognate plasma metabotype and could be used as putative indicators of increasing inflammation and severity over time.

FRI-417

Multi-omics analysis reveals the therapeutic effect and mechanism of the Chinese herbal JiGuCao capsule on acute alcoholic hepatitis in mice

Yue Chen[1], Hening Chen[1], Wenying Qi[1], Xu Cao[1], Ruijia Liu[1], Zao Xiaobin[1,2], Yong'an Ye[1,3]. *[1]Dongzhimen Hospital, Beijing University of Chinese Medicine, China; [2]Key Laboratory of Chinese Internal Medicine of Ministry of Education and Beijing, Dongzhimen Hospital, Beijing University of Chinese Medicine, China; [3]Institute of Liver Diseases, Beijing University of Chinese Medicine, China*
Email: chen.yue123456@163.com

Background and aims: Alcoholic hepatitis (AH) is a kind of alcohol-related liver disease (ALD), caused by alcohol abuse, with high morbidity and mortality, which increases the risk of liver falure, liver cirrhosis and hepatocellular carcinoma, and the current treatment methods are still limited. Its pathogenesis is closely related to inflammatory response, intestinal mucosal permeability changes, bile acid circulation disorders, and other mechanisms. Traditional Chinese medicine (TCM) has shown a therapeutic effect to treat AH. JiGuCao capsule (JGC) is a commonly used marketed TCM for the treatment of acute and chronic hepatitis. However, the therapeutic effect and mechanism of JGC in the prevention and treatment of AH are still unclear and need further study.

Method: A mouse model of AH was established with 14 days of 5% (v/v) ethanol liquid diet and a single dose of 31.5% (v/v) ethanol liquid diet gavage (Figure A). At the same time, the treatment group was given by gavage of an aqueous solution of JGC. The therapeutic effect of JGC on AH was determined by serological analysis of liver function and histopathological examination of hematoxylin-eosin (HE) and oil red (OR) staining. At the same time, transcriptomics and non-target metabolomics of liver tissues, and 16S ribosomal DNA sequencing (16S seq) of gut microbiota were used to investigate the protective effects of JGC on AH. The differently expressed genes (DEGs) and differently expressed metabolites (DEMs) between the model and the JGC groups were screed out to perform further enrichment analyses including the Gene Ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG).

Results: Compared with the model group, the intervention of JGC reduced serum levels of alanine aminotransferase and aspartate aminotransferase (Figure B). In histology and pathology, HE and OR staining showed that ethanol exposure significantly increased the number of steatosis and necrotic cells in the liver of the model group, and a large number of fat vacuoles appeared. Meanwhile, the villi structure of the small intestine was scattered, the cells were shed, and the small intestinal glands were increased. Compared with the model group, JGC alleviated hepatic steatosis and restored the integrity of the intestinal structure (Figure C). The enrichment analyses of DEGs showed that JGC may affect KEGG pathways of Bile secretion, retinol metabolism, fatty acid degradation, Gastric cancer and GO pathway of cellular response to interferon-beta, response to cytokine, symbiont-containing vacuole membrane, endoplasmic reticulum membrane, GTPase activity, GTP binding (Figure D–F). The enrichment analyses of DEMs showed that JGC could regulate amino acid metabolism, protein digestion and absorption, and ABC transporter pathways (Figure H–J). And in the gut microbiota level, the results of 16S seq showed that at the genus level, the JGC treatment restored the reduction of Lactobacillus content caused by alcohol, and increased the content of norank_f_Muribaculaceae and Prevotellaceae_UCG-001 (Figure K–L).

Conclusion: Histopathological and multi-omics analysis studies showed that JGC could have good preventive and therapeutic effect on AH.It could restore the normal function of the gut-liver axis by regulating the transport of bile acids and the ecological structure of intestinal flora. And JGC could effectively alleviate liver inflammation, restore the liver and intestinal injury caused by alcohol.

FRI-418

Strategies are needed to support people with alcohol use disorder and alcohol-related liver disease to take part in randomised clinical trials: results from the MIRAGE pilot trial of functional imagery training

Ashwin Dhanda[1,2], Victoria Allgar[1], Jackie Andrade[1], Lynne Callaghan[1], Benjamin Hudson[3], Wendy Ingram[1], Angela King[1], Victoria Lavers[4], Joe Lomax[1], Anne McCune[5], Crispin Musicha[1], Richard Parker[6], Christopher Rollinson[7], Siobhan Creanor[8].

[1]*University of Plymouth, Faculty of Health, Plymouth, United Kingdom;* [2]*University Hospitals Plymouth NHS Trust, South West Liver Unit, Plymouth, United Kingdom;* [3]*Royal Devon University Hospitals NHS Foundation Trust, United Kingdom;* [4]*Unaffiliated, United Kingdom;* [5]*University Hospitals Bristol and Weston NHS Foundation Trust, Department of Liver Medicine, United Kingdom;* [6]*Leeds Teaching Hospitals NHS Trust, United Kingdom;* [7]*University Hospitals Plymouth NHS Trust, Research Development and Innovation, United Kingdom;* [8]*University of Exeter, Exeter Clinical Trials Unit, United Kingdom*
Email: ashwin.dhanda@nhs.net

Background and aims: Treatment of alcohol use disorder (AUD) in people with alcohol-related liver disease (ARLD) reduces the risk of disease progression and mortality. However, there are no effective evidence-based therapies. Functional Imagery Training (FIT) is a novel therapy combining motivational interviewing techniques with imagery to strengthen motivation for behaviour change. We conducted a pilot trial of FIT to test whether people with AUD and ARLD could be recruited and retained in a trial and how well FIT could be delivered within the UK National Health Service (NHS).
Method: We conducted a multicentre randomised pilot trial of FIT with treatment as usual (TAU) versus TAU alone in patients with unplanned hospital admissions with AUD and ARLD. Primary outcomes were recruitment and retention rates. Secondary outcomes included self-reported alcohol use by timeline follow-back. Alcohol liaison nurses were trained to deliver FIT to participants who received the first session in hospital and a further 8 sessions over 6 months by phone. Follow-up of all participants was by phone for Days 28 and 90 and in-person at Day 180 (D180), the primary end point. To help retention, participants were asked to provide contact details for a nominated second person and offered a financial incentive at the final trial visit.
Results: Of 121 patients approached, 54 were recruited (45% recruitment rate) and randomised (TAU: 28; FIT+TAU: 26): mean (SD) age 49 (11), 63% male, 52% had cirrhosis with mean MELD 24 (6.5). Non-participation was mainly due to ineligibility (n = 11), lack of interest (n = 17) and logistical challenges (n = 28). 14 (26%) participants were not retained to D180 due to death (n = 5) and withdrawal (n = 9). Of the remaining 40 participants, 23 (58%) attended the D180 visit. 9, 17 and 17 participants did not attend trial visits at Days 28, 90 and 180, respectively. Most alcohol liaison nurses delivered FIT with adequate fidelity. 50% of participants randomised to FIT+TAU received the first 2 sessions (considered an adequate dose of the intervention). Based on all available data, median alcohol use per week fell from 1568 g (range 788, 2128) pure ethanol at baseline to 0 g (0, 180) at D180 and from 1120 g (610, 1784) to 0 g (0, 196) in TAU and FIT+TAU groups, respectively.
Conclusion: This study demonstrates the importance and challenges of recruitment and retention. Although we showed that alcohol workers in the UK NHS could successfully deliver FIT to people with AUD and ARLD, low retention limited interpretation of clinical outcomes. The implemented retention plan was inadequate as participants frequently changed phone number or did not respond to calls. Robust strategies to support recruitment and retention of people with AUD and ARLD must be incorporated in future clinical trials to enable the evaluation of new interventions in this under-served patient population.

FRI-419
Supplementation of choline attenuates the onset of alcohol-related liver disease

Victor Sánchez[1], Anja Baumann[1], Franziska Kromm[1], Annette Brandt[1], Ina Bergheim[1]. [1]*University of Vienna, Department of Nutritional Sciences, Austria*
Email: ina.bergheim@univie.ac.at

Background and aims: Alcohol-related liver disease (ALD) is still one of the most common liver diseases worldwide. Besides altering liver

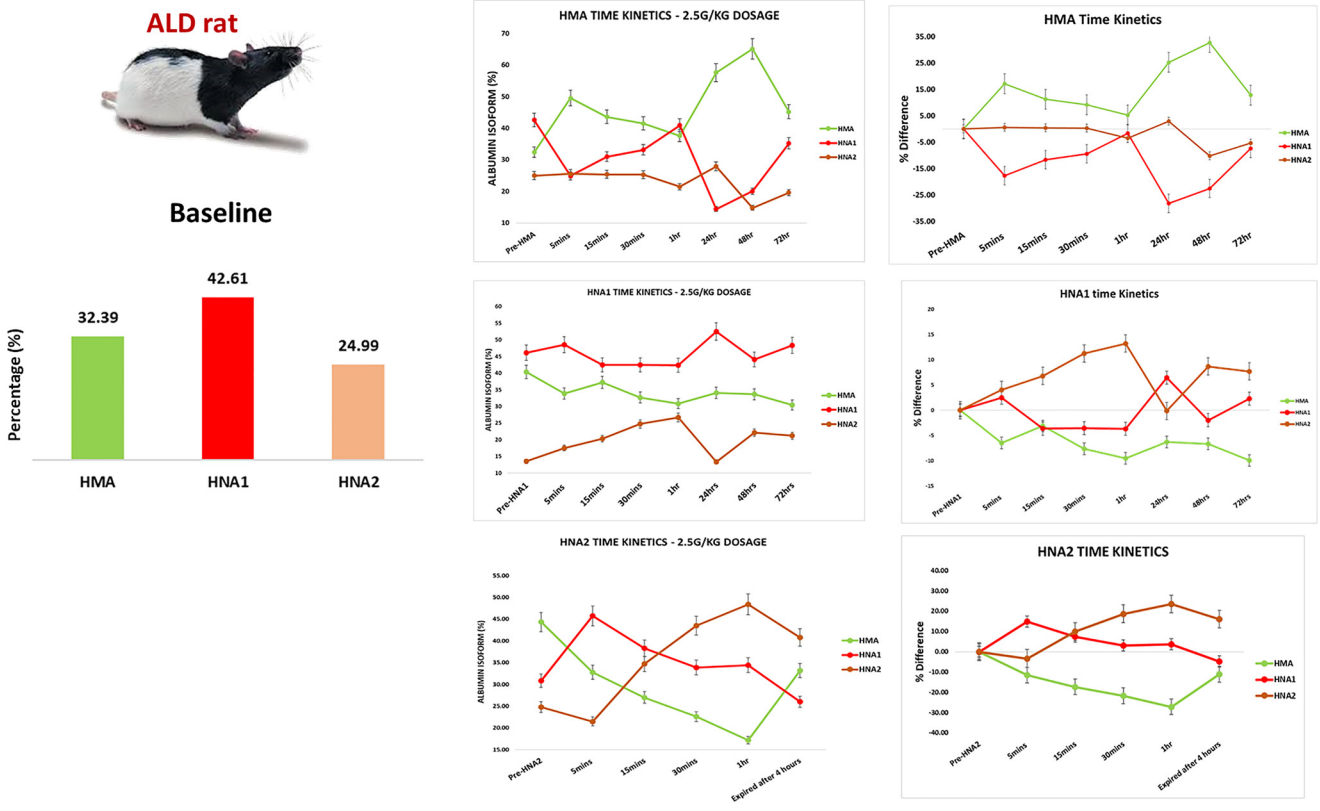

Figure: (abstract: FRI-416).