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PWE-290 ACTIVE ALCOHOL CONSUMPTION INDUCES FUNCTIONAL IMMUNE PARESIS BUT PARADOXICALLY PROMOTES ENDOTOXIN TOLERANCE IN THOSE WITH ADVANCED ALCOHOL-RELATED CIRRHOSIS

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Introduction Patients with alcohol-related cirrhosis (ARC) are particularly prone to infection which is frequently a precipitant of organ failure and death. Neutrophil dysfunction has been reported in patients with ARC. Sepsis and associated endotoxemia occur in approximately 40% of hospitalised patients. Neutrophil TLRs are able to sense pathogens and induce inflammatory responses but whether active alcohol drinking is protective or detrimental in this context remains unknown. The aim of this study was to characterise the neutrophil phenotype, TLR2/4/9 expression and plasma cytokine profile in patients with ARC who were abstinent (n=13) compared to those who were drinking (n=16), split by MELD score 15 compared to healthy controls (n=12).

Methods Neutrophils isolated from patients with ARC were studied ex vivo at baseline, and following 2-h stimulation with lipopolysaccharide (LPS) and the bacterial degradation protein fMLP. Neutrophil phenotype and TLR expression were determined using anti-CD16 (PE); -CD11b (APC-Cy7); -TLR2 (Alexa Fluor 488); -TLR4 (biotin conjugated PE-Cy7 Streptavidin) and -TLR9 (APC) by flow cytometry. Intracellular cytokine production pre- and post-stimulation will be measured by CBA.

Results The severity of cirrhosis (MELD15) or abstinent/active drinking status did not significantly impact on resting CD16, CD11b, TLR2 and 9 expression. TLR 2/9 expression on exposure to LPS and fMLP showed downregulation in those who were active alcohol-drinkers compared to the baseline. Conversely TLR4 expression was upregulated in the abstinent group with MELD >15; an effect significantly abrogated by the effect of active drinking (p=0.004). Active alcohol consumption did not however change TLR4 expression in those with MELD.

Conclusion Active alcohol consumption was shown to downregulate functional TLR2/9 expression resulting in immunoparesis with potential susceptibility to Gram-positive infection. However, active alcohol consumption was shown to abrogate the increased TLR4 responses to endotoxin stimulation seen in the abstinent ARC cohort with MELD >15. This implies that alcohol paradoxically promotes endotoxin tolerance and may act as a potential protective mechanism against Gram-negative insults in those with advanced cirrhosis.

Competing interests None declared.

PWE-291 MAPK SIGNALLING REGULATES THE DEVELOPMENT OF A CHOLANGIOCELLULAR PHENOTYPE FROM HCC IN POST-TACE LIVER TRANSPLANTS

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Introduction During normal liver wound-healing, tissue injury causes inflammation and cell death, which in turn orchestrates compensatory cell proliferation and regeneration.¹ If resolution of the injury cannot be obtained the resulting unchecked healing process can lead to cancer. Similar injury-induced repair mechanisms occur in response to chemotherapeutic treatments.¹ We recently found that the use of pre-transplantation TACE for HCC promotes the development of a mixed cholangiocellular phenotype that is associated with the expression of CD133, a marker of hepatic progenitor cells (HPC). This phenomenon is associated with higher post-transplantation tumour recurrence.² The molecular bases for the development of the cholangiocellular phenotype have not been investigated before. In this study we identified key oncogenic effectors involved with a "switch" from HCC to cholangiocellular phenotype resulting from liver injury induced by TACE treatment.

Methods Ten cases of post-TACE (doxorubicin/lipiodol) treated HCC examined after transplantation at King's College Hospital were selected for the study. HCC patients not treated by TACE before transplantation were used as control group. Formalin-fixed section from main tumour mass embedded in paraffin blocks were used to perform immunohistochemistry in order to delineate which component of the MAPK signalling pathway is associated with the hepatocholangiocellular phenotype and expression of HPC markers (CD133 and CK19).

Results Among the post-TACE liver explants, approximately 50% of the neoplastic cells resembling bile ductules (cholangiocellular differentiation) showed nuclear expression of a specific phospho-activated component of the MAPK cascade. Furthermore, half of the cells positive for activated-MAPK showed proliferative activity, as determined by Ki67 staining. Expression of activated-MAPK was not detected in the non-TACE treated group of liver transplant.

Conclusion The development of the mixed hepato-cholangiocellular phenotype in HCC patients after TACE-inflicted liver injury relates to activation of a specific MAPK signalling pathway that promotes proliferation of HPC. Attenuation of this signalling pathway could be used to prevent the "uncontrolled" proliferation and differentiation of progenitor cells before liver transplantation in HCC patients, and thus improving the tumour recurrence rate.

Competing interests None declared.

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PWE-292 NAFLD: BELOW THE RADAR EVEN ON SURFACING IN SECONDARY CARE!

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Introduction Non-alcoholic fatty liver disease (NAFLD) is becoming a common cause for secondary care referral. While simple steatosis does not lead to liver related morbidity, non-alcoholic steatohepatitis (NASH) may lead to cirrhosis and hepatocellular carcinoma. Currently, non-invasive imaging including ultrasonography (USS) may reveal fatty infiltration. Many patients attend secondary care for USS, in whom NAFLD may be identified incidentally. While the true prevalence and burden of NAFLD in the community remains unclear, patients attending for USS in whom NAFLD is identified could provide the opportunity to reduce disease burden by monitoring for any complications. The aims of this study were to assess