P59 TLR4 ANTAGONIST IN ACUTE LIVER FAILURE: A NOVEL THERAPEUTIC STRATEGY

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Introduction Acetaminophen (APAP) toxicity is the commonest cause of acute liver failure (ALF) which is characterised by multi-organ failure manifested by rapid acute liver injury, severe brain oedema and renal failure. Without liver transplantation, about 40% patients die and its treatment is an unmet medical need. Unregulated inflammatory response plays an important role in its pathogenesis. A multitude of cytokines are released during ALF with consequent activation of NfKB and progressive liver injury. We hypothesised that Toll-like receptor-4 may be critical in the progression to multiorgan failure.
Aim The aim of this study was to determine whether administration a novel TLR4 antagonist (STM28) to an APAP model of ALF in mice would prevent liver injury and its deleterious effect on the brain and the kidneys. (STM28 was kindly gifted by Professor Ken-ichi Tanamoto, Division of Microbilogy, National Institute of Health Sciences, Tokyo 158-8501, Japan).
Method Three groups of Cd1 male mice were studied. Sham, APAP (acetaminophen, 500 mg/kg single dose IP after over night fasting), APAP+TLR4 antagonist (STM28; 20 ug IP, 1 h prior to the administration of APAP and 6 h later). All the mice were hydrated, administered 10% dextrose and kept in temperature controlled environment. Blood was collected for biochemistry and cytokine assay. Liver, kidney and brain were collected for western blotting and cytokine analyses and the brain frontal cortex for brain water. Animals were sacrificed at 12 h after APAP administration.
Results Administration of APAP led to an increase in the level of liver enzymes, ALT ($p=0.004$) and AST ($p=0.007$) in comparison to the Shams, which was significantly reduced (ALT ($p=0.01$) and AST ($p=0.008$)) in the TLR4 antagonist group. ALF associated increase in ammonia ($p=0.001$) and brain water ($p=0.04$) were significantly reduced (ammonia ($p=0.03$); brain water ($p=0.05$)). ALF associated renal failure ($p=0.004$) was also markedly attenuated ($p<0.09$). Protein expression of NFkBp65 on western blot showed an increased expression in brain and kidney ($p=0.03$) and ($p=0.02$) respectively which was reduced to values that were not significantly different to Sham levels (brain ($p=0.04$) and kidney ($p=0.02$)). The expression of NFkBp65 protein expression on western blot in liver was down-regulated in ALF compared with sham ($p=0.01$) animals and restored in TLR4 antagonist group Sham values ($p=0.02$).
Conclusion The results of this study show for the first time a role for TLR4 in pathogenesis of multiorgan failure in ALF. The data strongly support a potential therapeutic role for TLR4 antagonist in the prevention of progression of ALF.

P60 ACUTE LOWERING OF PORTAL PRESSURE IN CIRRHOTIC RATS BY ANTI-TNF THERAPY IS ASSOCIATED WITH REDUCED NFKB-DRIVEN INFLAMMATION AND IMPROVED ENOS FUNCTION THROUGH THE ASYMMETRIC DIMETHYLARGININE-DIMETHYLARGININE-DIAMINOHYDROLASE AXIS

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Introduction Anti-TNF (Infliximab) monotherapy has been shown to reduce hepatic inflammation and lower portal pressure in alcoholic hepatitis patients. Although the side effect profile of Infliximab limits its clinical use in these patients, ongoing study of the mechanism of this profound beneficial effect remains important to determine novel pathways and future therapeutic targets.
Aim This study aimed to determine whether reduction of NFkB and its target gene TNFα by Infliximab has favourable effects upon the asymmetric dimethylarginine-dimethylarginine-diaminohydrolase (ADMA-DDAH) axis, increasing NO availability whilst lowering portal pressure in bile duct ligated (BDL) cirrhotic rats.
Method Sham (n=6) and BDL (n=15) rats were compared 4 weeks after BDL surgery (treated with vehicle), and in an additional BDL group (n=6) 72 h after 10 mg/kg daily intraperitoneal Infliximab. Rats underwent direct portal pressure assessment under terminal anaesthesia.
Measurements Plasma ALT (Cobas-Integra analyser); hepatic ADMA (LC/MS/MS); eNOS activity (radiometric assay). Hepatic protein expression for NFkB, TNF-α, inducible NOS (iNOS), 4-hydroxy nonenol (HNE) and DDAH-1 were measured by western blot.
Results ALT was significantly ($p<0.0001$) higher in BDL rats compared to sham, and reverted to near normal following anti-TNF treatment ($p<0.05$). Protein expressions for NFkB, its target gene TNF-, iNOS and 4HNE were all significantly increased ($p<0.01$; $p<0.03$; $p<0.01$; $p<0.01$, respectively) in BDL rat livers compared to sham. Infliximab administration significantly reduced expression of NFkB, TNF-α, iNOS and 4HNE ($p<0.03$; $p<0.03$; $p<0.05$; $p<0.05$, respectively) compared with vehicle treated BDL. Moreover, hepatic DDAH-1 protein was significantly decreased in BDL rats compared to sham ($p<0.01$) but this normalised to sham levels after Infliximab. Hepatic ADMA was significantly higher in BDL compared with sham ($p<0.0001$) and reverted back to sham levels ($p<0.001$) following anti-TNF therapy. Reduction of inflammatory signalling following anti-TNF therapy restored eNOS activity associated with a significant lowering of portal pressure compared to vehicle treated BDL rats (9.48 ± 0.7 vs13.5 ± 0.6 mm Hg respectively, $p=0.001$).
Conclusion This study confirms significant lowering of portal pressure following Infliximab therapy in the BDL model of cirrhosis. This beneficial effect is associated with reduced hepatic inflammation and restoration of the abnormal ADMA-DDAH-eNOS axis providing potential new targets for portal hypertension therapy.

Viral hepatitis

P61 PEGYLATED INTERFERON AND RIBAVARIN COMBINATION THERAPY ACHIEVES HEPATITIS E VIRUS CLEARANCE IN CHRONIC HEPATITIS E VIRUS/HUMAN IMMUNODEFICIENCY VIRUS CO-INFECTION

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Introduction Chronic hepatitis E virus (HEV) infection, with rapidly progressive cirrhosis, has recently been documented in immunosuppressed solid organ transplant recipients. In this setting HEV viral clearance can be achieved by either reducing the dose of immunosuppressive agents or by the use of pegylated interferon and/or ribavarin. Chronic HEV infection has also been observed in patients co-infected with human immunodeficiency virus (HIV).[1] Acute and chronic HEV is sometimes associated with sensory/motor neuropathy.
Aim To describe the clinical and laboratory features of HEV/HIV co-infection, and response to antiviral therapy.
Method A 48-year-old bisexual male was found to be infected with HIV-1 in 2001. In 2003 he was treated for military tuberculosis. Following this he developed a painful, progressive sensory peripheral neuropathy affecting the lower limbs. In 2007 he was noted to have

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