

Descartes, INSERM Unité 567, and Assistance Publique Hopitaux de Paris, Cochin Hospital Paris, France; <sup>5</sup>Alamo Medical Research, San Antonio, Texas, USA; <sup>6</sup>Hospital General de Valencia, Valencia, Spain; <sup>7</sup>Department of Gastroenterology, Alfred Hospital, Melbourne, Australia; <sup>8</sup>Emilio Ribas Infectious Diseases Institute, Sao Paulo, Brazil; <sup>9</sup>Center for Liver Disease, Inova Fairfax Hospital, Falls Church, Virginia, USA; <sup>10</sup>Medical University of Warsaw, Wolska, Warsaw, Poland; <sup>11</sup>Tibotec BVBA, Beerse, Belgium; <sup>12</sup>Tibotec Inc., Titusville, New Jersey, USA

**Introduction** This Phase 3 study evaluated telaprevir (T) in combination with pegylated-IFN alfa-2a (P) and ribavirin (R) in well-characterised G1 prior-PR treatment failure patients including prior PR non-responders (null and partial) and relapsers.

**Method** REALIZE was a randomised, international, multicentre, double-blind, placebo-controlled trial evaluating efficacy, safety and tolerability of T (750 mg q8 h) plus P (180µg/w) and R (1000–1200 mg/d) compared with PR alone. The treatment arms (randomised 2:2:1, stratified by viral load and prior response) were: 12-weeks T/PR, followed by 36-weeks PR (T12PR48); 4-weeks PR followed by 12 weeks T/PR (T delayed start, DS), then 32-weeks PR (T12(DS)/PR48); 48-weeks PR (Pbo/PR48). The primary objective was efficacy of the T/PR arms in non-responders and relapsers. Secondary objectives included evaluation of T DS and efficacy in prior-null and -partial responders. HCV RNA was quantified using COBAS TaqMan<sup>®</sup> v2.0 assay (LLOQ=25 IU/ml).

**Results** 833 patients were screened, and 662 treated. 70% of patients were male, 93% Caucasian, 26% had cirrhosis, and 89% had baseline HCV RNA ≥800 000 IU/ml. AEs reported more frequently in T arms were rash, pruritus, diarrhoea, anorectal disorders and anaemia. 13% of T/PR patients had premature discontinuation (D/C) of T due to AEs: rash (4%) and anaemia (3%) were the most common AEs leading to T D/C.

**Conclusion** T/PR SVR was significantly superior to PR in all prior-treatment failure populations including null- and partial-responders. A telaprevir delayed start did not have a significant impact on SVR rates. Safety profile of T/PR was consistent with that observed in treatment naive subjects.

Abstract OP03 Table 1

	T12/PR48	T12 (DS)/PR48	Pbo/PR48
% Relapsers			
	N=145	N=141	N=68
SVR**	83 (<0.001)	88 (<0.001)	24
(p value*)			
Prior PR Non-responders			
	N=121	N=123	N=64
SVR**	41 (<0.001)	42 (<0.001)	9
(p value*)			
Partial-responders			
	N=49	N=48	N=27
SVR**	59 (<0.001)	54 (<0.001)	15
(p value*)			
Prior PR null-responders (<2 log decline in HCV RNA at wk 12 of prior therapy)			
	N=72	N=75	N=37
SVR**	29 (<0.001)	33 (<0.001)	5
(p value*)			

\*In comparison to Pbo/PR48.

\*\*Assessed 24 weeks after planned treatment completion.

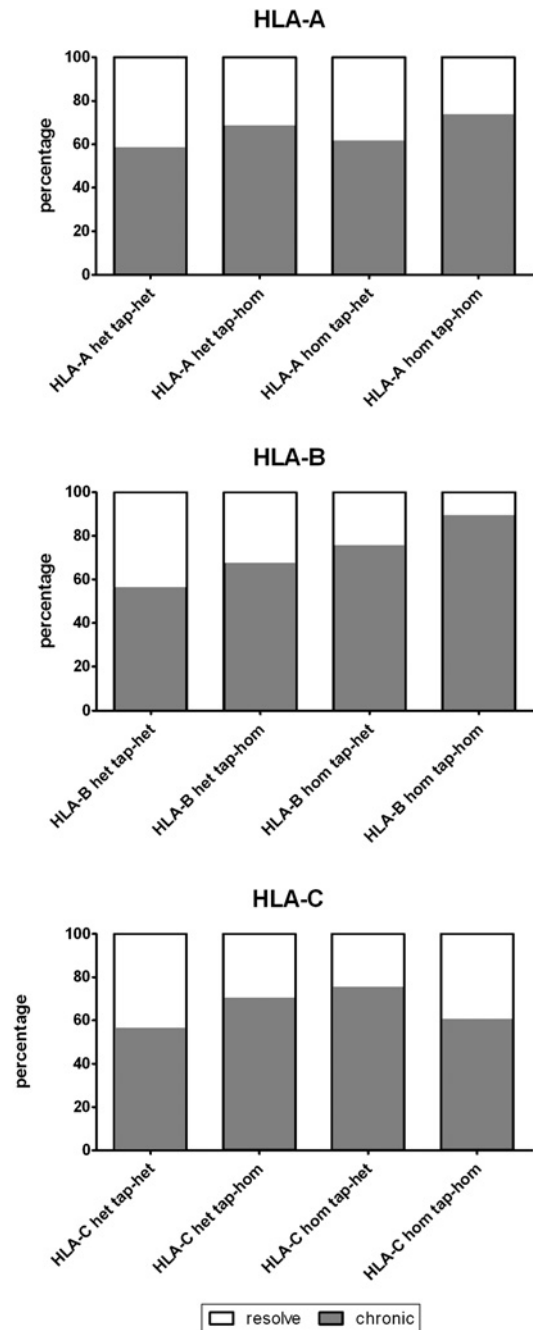
**OP04 SYNERGISTIC INFLUENCE OF TAPASIN AND HLA CLASS I PROTECTION AGAINST CHRONIC HEPATITIS C VIRUS INFECTION**

doi:10.1136/gutjnl-2011-300857b.4

<sup>1</sup>S Ashraf, <sup>1</sup>S Knapp, <sup>1</sup>C Bectford-Tackoir, <sup>2</sup>C Brooks, <sup>3</sup>A-M Little, <sup>4</sup>G Alexander, <sup>5</sup>M Cramp, <sup>1</sup>S I Khakoo. <sup>1</sup>Department of Hepatology, Division of Medicine, Imperial

College London, UK; <sup>2</sup>Centre for Public Health Research, Massey University, Wellington, New Zealand; <sup>3</sup>Laboratory of Histocompatibility and Immunogenetics, Gartnavel General Hospital, Glasgow, UK; <sup>4</sup>Department of Medicine, University of Cambridge, UK; <sup>5</sup>Hepatology Research group, Peninsula Medical School, Derriford Hospital

**Introduction** HLA class I is associated with the outcome of hepatitis C virus (HCV) infection. Tapasin is a member of the peptide loading complex that loads self and viral peptides onto HLA class I. Presentation of viral peptides by HLA class I is critical in generating an effective cytotoxic T lymphocyte (CTL) response, and hence in clearing HCV infection. However, not all HLA alleles require tapasin for efficient peptide loading. Thus polymorphisms in the tapasin gene could affect clearance of HCV in combination with specific “tapasin-dependent” HLA class I alleles. The SNP rs2071888 is a



Abstract OP04 Figure 1 Association Of tapasin and HLA-B Heterozygosity with resolution of hepatitis c infection (p=0.005(trend test)). protection was not significantly associated with heterozygosity at HLA-A or HLA-c and tapasin.

non-synonymous polymorphism in exon 4 of the *Tapasin* gene causing an arginine to threonine change that could affect tapasin function. We have investigated the effect of this SNP in resolving hepatitis C virus (HCV) infection in a cohort of 336 patients from the UK.

**Aim** We have investigated the effect of the SNP rs2071888 in resolving hepatitis C virus (HCV) infection in a cohort of 336 patients from the UK.

**Method** Genomic DNA from 216 chronically infected individuals and 120 spontaneous resolvers of HCV was genotyped with an allele specific PCR designed to identify the G/C SNP in exon 4 of the *Tapasin* gene. Individuals were also typed for HLA-A, -B and -C. Results were analysed for association with hepatitis C outcome.

**Results** Overall the G allele of tapasin was associated with protection against chronic HCV infection ( $p=0.018$ , OR=1.99, 95% CI 1.14 to 3.46). Interestingly, in combination with heterozygosity at the HLA-B locus, heterozygosity at the tapasin locus was also protective (Abstract OP04 figure 1,  $p$  trend =0.005). Furthermore, we identified specific HLA-B alleles associated with protection in the context of the Tapasin G, but not Tapasin C allele. Specifically the G allele was most protective in the context of B\*0702 ( $p=0.029$ , OR=4.56, 95% CI 1.2 to 17.27), and B\*5701 ( $p=0.029$ , OR=12, 95% CI 1.2 to 120). Tapasin has been shown to bind specifically to amino acids 114 and 116 of HLA class I. Consistent with this functional interaction we found that aspartate at position 114 and serine at 116 were most beneficial in the context of both the G allele (D114/TapG,  $p<0.0001$ , OR=3.3, 95% CI 1.83 to 5.98; S116/TapG,  $p<0.0001$ , OR=2.73, 95% CI 1.57 to 4.76).

**Conclusion** The G allele of tapasin was associated with protection from chronic HCV infection, both alone and in combination with specific HLA class I alleles. Individuals who are heterozygous for both tapasin and HLA-B are relatively protected from chronic HCV infection. This heterozygosity may allow them to present a broader range of peptides to CTL and thus mount a more effective anti-HCV immune response.

## Transplant

### OP05 THE IMPACT OF COMORBIDITIES ON OUTCOME OF PATIENTS ASSESSED FOR LIVER TRANSPLANTATION, WAITING LIST MORTALITY AND POST LIVER TRANSPLANTATION SURVIVAL USING THE CHARLSON COMORBIDITY INDEX

doi:10.1136/gutjnl-2011-300857b.5

M A B Al-Freah, E Dionigi, L Blackmore, E Johnston, A Zubir, M Foxton, W Bernal, G Auzinger, M Rela, N D Heaton, J G O'Grady, M A Heneghan, J A Wendon. *Institute of Liver Studies, King's College Hospital, London, UK*

**Introduction** Severity of liver disease determines accurately the outcome of patients on liver transplant (LT) waiting list (WL). Comorbidities are known to affect post-LT outcomes but their effect on outcome of transplant assessment (TA) or WL mortality have not been fully explored in previous studies.

**Aim** To study the impact of comorbidities on TA, WL mortality and post LT survival.

**Method** Retrospective study of all patients assessed for LT at our centre between 1 January 2000 and 31 December 2007 ( $n=1484$ ). Patients with acute liver failure (175), amyloid (43), those assessed for re-LT (149) and 24 with incomplete information were also excluded. Nine comorbidities (Charlson Comorbidity Index - CCI) were prospectively defined according to Volk *et al* (*Liver Transplant* 2007;13:1515–20). Kaplan–Meier analysis was performed to determine impact of comorbidity on outcome. Cox regression hazard analysis was used to determine predictors of outcome and presented as (OR, 95% CI,  $p$  value).

**Results** We analysed 1093 patients. Median age was 54 years (17–84), 67.5% were men (738). There were 192 (17.6%) patients

with hepatocellular carcinoma (HCC). Patients with  $\geq 1$  comorbidity were 499 (46.6%) with most common comorbidities being diabetes (23.2%) and renal dysfunction (12.1%). Of 1093 assessed patients, 826 (75.6%) were listed. Patients with  $\geq 1$  comorbidity had significantly decreased LT free survival (log rank =33.586,  $p<0.001$ ). Multivariate analysis showed CCI (1.79, 1.52 to 2.11,  $p<0.001$ ), age (1.03, 1.00 to 1.05,  $p=0.035$ ), Na (0.93, 0.89 to 0.97,  $p=0.001$ ), MELD (1.10, 1.06 to 1.14,  $p<0.001$ ) as being predictive. Of those listed for LT (826), 600 (72.6%) were transplanted, 161 (19.5%) died on WL and 65 (7.9%) were delisted. Listed patients with  $\geq 1$  comorbidity had significantly decreased LT free survival (log rank =9.045,  $p=0.003$ ). Multivariate analysis showed CCI (1.79, 1.52 to 2.11,  $p<0.001$ ), age (1.02, 1.01 to 1.03,  $p=0.006$ ), pre-LT Hb level (0.87, 0.80 to 0.95,  $p=0.003$ ), Na (0.96, 0.93 to 0.99,  $p=0.014$ ) and MELD (1.14, 1.11 to 1.18,  $p<0.001$ ) were predictors of listing outcome. Transplanted patients with  $\geq 1$  comorbidity had significantly decreased post LT survival (Log rank =7.645,  $p=0.006$ ). Multivariate analysis showed that only CCI (1.36, 1.13 to 1.64,  $p=0.001$ ) and HCC (1.74, CI 1.21–2.51,  $p=0.003$ ) were independently associated with post-LT mortality. Similar post LT survival results seen when CCI was divided into 0, 1 and  $\geq 2$  comorbidities (Log rank =11.342,  $p=0.003$ ).

**Conclusion** We demonstrate that comorbidities significantly impact on the outcome of patients with chronic liver disease at TA, on wait-list and post LT survival. Adding CCI to known liver prognostic models may improve their prediction ability.

## Basic science

### OP06 MATERNAL OBESITY PROGRAMS OFFSPRING INNATE IMMUNE DYSREGULATION IN NON-ALCOHOLIC FATTY LIVER DISEASE

doi:10.1136/gutjnl-2011-300857b.6

<sup>1</sup>A Mouralidarane, <sup>1</sup>J Soeda, <sup>2</sup>Anne-Maj Samuelsson, <sup>2</sup>P Taylor, <sup>2</sup>L Poston, <sup>1</sup>J A Oben. <sup>1</sup>University College London, UK; <sup>2</sup>King's College London, UK

**Introduction** Obesity induced, non-alcoholic fatty liver disease (NAFLD), is the major cause of chronic liver dysfunction. In tandem, obesity and NAFLD rates in reproductive age women are rising. We have previously reported increased susceptibility to NAFLD in offspring exposed to maternal obesity via programming.

**Aim** Our aim is to investigate the effects of maternal obesity on hepatic innate immune function in a more physiologically relevant model of NAFLD.

**Method** Female mice were fed standard or obesogenic chow, before, throughout pregnancy and in lactation. Offspring were then weaned onto either standard or obesogenic chow and studied at 3, 6 and 12 months. Read-outs included biochemical and histological indicators of NAFLD and fibrosis, hepatic triglycerides, gene expression analysis of pro-fibrotic pathways, FACS analysis of liver innate immune cells and flow cytometric detection of ROS.

**Results** Offspring only exposed to a post-weaning hyper-caloric diet (Group 2) exhibited raised leptin, ALT and hepatic triglyceride content compared to controls (Group 1) ( $p<0.001$ ). Moreover, hepatic gene expression of injury and fibrogenic markers were increased (Abstract OP06 table 1,  $p<0.01$ ). As expected, a more robust phenotype was observed at 12 compared to 3 months. Additionally, offspring exposed to maternal obesity plus a post-weaning hyper-caloric diet (Group 3), displayed a more profound NAFLD phenotype with development of fibrosis and a NAFLD Activity Score  $>5$ . Mechanistically, we observed increased Kupffer cell numbers with impaired phagocytic function and raised ROS production, alongside reduced NKT cell numbers, in Group 3 compared to Group 1 ( $p<0.01$ ).