BASL: Oral presentations
Thursday 8th September 2011
Clinical hepatology

OP01 WHO DIES FROM ALCOHOLIC LIVER DISEASE AND WHERE ARE POSSIBLE THERAPEUTIC INTERVENTIONS MISSED? AN ANALYSIS OF 755 DEATHS IN A HEALTH COMMUNITY 2007–2010

doi:10.1136/gutjnl-2011-300857b.1

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Introduction The mortality from alcohol related liver disease in the UK has more than doubled in the last decade. Services to assist people with alcohol related health problems are available but identification of those at risk of avoidable mortality remains poor.
Aim To establish the demographic details of people dying of alcohol related liver disease in a health community, determine trends and demographic associations with ALD mortality and ascertain secondary healthcare systems attendances (and reasons for them) prior to death. These are settings where alcohol interventions may be offered.
Method Identification of ALD related deaths was established via Public Health Mortality Data (ONS) and Hospital Episode Statistics for in-patient and Emergency Department attendances. Deprivation (Index of Multiple Deprivation, IMD) and population mosaic data are available for the local communities studied.
Results 755 people died with a primary or underlying diagnosis of ALD from 2007 to 2010. Mortality rates overall are stable over this time period. Age at death was 20–34 in 2.4%, 35–39 in 24%, 50–64 in 39%, 65–79 in 25% and 80+ in 10%. Standardised mortality rates (DSR) varied by geographical area from 18 (CI 13 to 23) to 46 (CI 40 to 52) and there was a strong correlation with social deprivation (R^2=0.83) but people dying of ALD had higher deprivation scores that their local population across all geographical areas (Mean IMD score general population 21.8 vs ALD 25.9, p=0.001). Mosaic groups at highest risk of ALD death varied by geographical area, in the highest mortality area, young, well-educated city dwellers and families in low-rise social housing with high levels of benefit need have the highest number of deaths but in these groups the mortality from ALD was relatively under-represented in comparison to the proportion of population in those groups (44% of population in those groups, 32% of ALD deaths) whereas the ALD deaths were over-represented in other mosaic groups (Elderly people reliant on state support, Young people renting flats in high density social housing and Residents with sufficient incomes in right-to-buy social houses, 40.76% of ALD deaths but 19.7% of population). 72% of deaths from ALD were in hospital, 24% at home with the remainder being in another community setting. Hospice care was rare (0.13%). 95% of people who died had a previous hospital admission prior to death but only 42% had a previous hospital admission with a diagnosis of ALD. 80% of ALD deaths had a prior Emergency department attendance. In those people with a prior hospital admission 32% had a discharge diagnosis of ALD suggesting that already advanced liver disease is not diagnosed or coded in 68% of hospital attendees in other specialty areas. The admissions were in a wide variety of specialty groups the most common being cardiac disease (7.9%), neoplasia (6.4%), injury/poisoning (6.3%) and mental and behavioural disorders (5.6%). There was a mean of 7.06 hospital admissions per death from ALD in the 5 years preceding death.
Conclusion Death from ALD is preceded by a substantial number of medical attendances in secondary care with the opportunity for intervention. Liver disease is unsuspected in a significant number of people in contact with secondary care. Mortality rates over a 4-year period remain high and cluster in particular demographic groups which has importance for public health interventions.

OP02 THE FIRST NEW MONOTHERAPY THERAPEUTIC PBC STUDY IN A DECADE? AN INTERNATIONAL STUDY EVALUATING THE FARNESOID X RECEPTOR AGONIST OBETICHOLIC ACID IN PBC

doi:10.1136/gutjnl-2011-300857b.2

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Introduction Obeticholic Acid (OCA), 6-ethyl chenodeoxycholic acid (CDCA) or INT-747, is a novel derivative of the primary human bile acid CDCA, the natural ligand for the farnesoid-X receptor. OCA has ~100x more FXR agonist potency than CDCA and in preclinical studies shows choleretic and anti-fibrotic properties. A prior primary biliary cirrhosis (PBC) study showed that OCA 10–50 mg, achieved highly statistically significant reductions in alkaline phosphatase (AP), GGT and ALT when added to ursodeoxycholic acid.
Aim To undertake an international, double blind, placebo (Pbo) controlled, parallel group, dose response study evaluating the effects of OCA in PBC.
Method Double blind, placebo (Pbo) controlled, parallel group, dose response study to explore effects on AP, other liver enzymes and safety in patients with PBC and persistently high AP levels (≥1.5–10× the upper limit of normal (ULN)) who had not been taking UDCA for at least 6 months. 59 patients received placebo, OCA 10 mg or 50 mg once daily for 12 weeks. All patients had definite (54%) or probable (46%) PBC; mean age was 55±1 years; female: 85%, Caucasian: 95%. Key pre-treatment values (mean±SEM): AP: 433±31 (female ULN: 117) U/l; GGT: 527±48 (female ULN: 50) U/l; ALT: 81±6 (ULN: 67) U/l; AST: 68±4 (ULN: 50) U/l.
Results Efficacy End of study changes (from pre-treatment). The 10 mg group showed an AP decrease from 3.9× ULN pre-treatment to 1.9× ULN at the end of the study.
Results - Safety Pruritus was the most common Adverse Experience (AE): Pbo: 30%, 10 mg: 70%, 50 mg: 94%; pruritic severity and discontinuation rate (Pbo: 0%, 10 mg: 15%, 50 mg: 38%) increased with dose. Other AEs were not clearly more commonly seen with OCA therapy. There was one serious AE in a placebo patient.
Conclusion OCA is the first rationally developed drug for cholestatic liver disease and shows substantial efficacy as a treatment for PBC as a single agent. Based on these data, a direct comparison with UDCA seems merited.

Abstract OP02 Table 1

Mean±SEM	? % AP	? AP ? U/l	% ? GGT	% ? ALT
Pbo (n=23)	+0.4±3.2	+11.7±13.1	−3±5	−4±9
OCA 10 mg (n=20)	−44.5±5.5***	−233.5±47.5***	−73±4***	−37±8**
OCA 50 mg (n=16)	−37.6±5.3***	−161.3±32.4***	−65±6***	−35±7**

**p<0.01, ***p<0.0001

Viral hepatitis

OP03 TELAPREVIR-BASED THERAPY IN G1 HCV-INFECTED PATIENTS WITH PRIOR NULL RESPONSE, PARTIAL RESPONSE OR RELAPSE TO PEGINTERFERON/RIBAVIRIN: REALIZE TRIAL FINAL RESULTS

doi:10.1136/gutjnl-2011-300857b.3

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

*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

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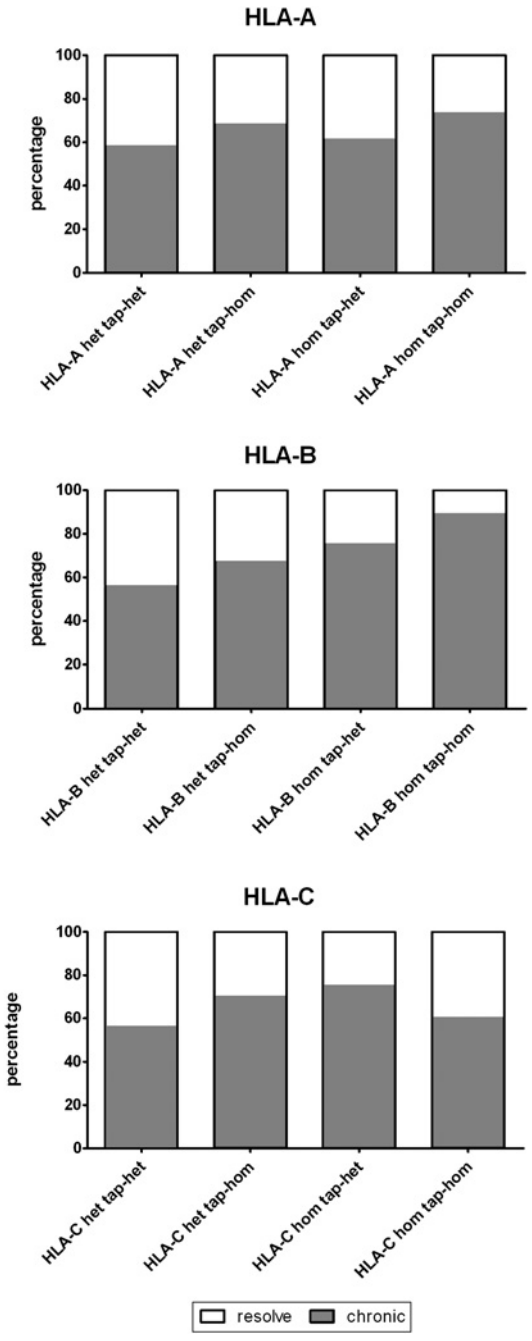
Introduction HLA class I is associated with the outcome of hepatitis C virus (HCV) infection. Tapasin is a member of the peptide loading complex that loads self and viral peptides onto HLA class I. Presentation of viral peptides by HLA class I is critical in generating an effective cytotoxic T lymphocyte (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 resoution of hepatitis c infection (p=0.005(trend test)). protection was not significantly associated with heterozygosityat HLA-A or HLA-c and tapsain.