

and continued their randomized treatment for a maximum of 12 weeks. A follow-up visit was performed 4 weeks after last dose of study drug. The primary endpoint was defined as an increase in platelet count to $\geq 100,000/\mu\text{l}$ at Week 4. **RESULTS** The highest response rate at Week 4, with respect to platelets, was observed in the 75mg eltrombopag group (20/21, 95%, $p < 0.0001$). Of the 49 subjects successfully initiating IFN therapy at Week 4, 5-15 subjects (36-65%) in the eltrombopag groups completed 12 weeks of antiviral therapy compared to 1 (6%) subject in the placebo group. Two SAEs were reported on treatment and 4 during follow-up; only one (thrombocytopenia) was considered related to study drug. The most common AEs during Part 1 were headache, dry mouth, nausea, diarrhoea. During Part 2, the most common AEs were events associated with systemic IFN therapy. **CONCLUSION** Eltrombopag increased platelet counts in all treatment groups at Day 28 and enabled 71%-91% of subjects to initiate antiviral therapy, with 36-65% of subjects completing 12 weeks of antiviral therapy. These data support further evaluation of eltrombopag in this patient population.

Disclosures:

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	Placebo N=18	30mg N=14	50mg N=19	75mg N=23
Median age (yrs)	52	56	50	51
Male gender (n/N, %)	11/18 (61%)	10/14 (71%)	12/19 (63%)	19/23 (83%)
Median platelet count at Baseline, $\times 10^3/\mu\text{l}$ (min, max)	55 (31,75)	61 (34,94)	53 (26,66)	55 (28,75)
Median platelet count at Week 4, $\times 10^3/\mu\text{l}$ (min, max)	52.5 (34,74)	136.5 (40,528)	213.5 (47,499)	209 (78,527)
Subjects with platelet count $\geq 100 \times 10^3/\mu\text{l}$ Week 4 (n/N, %)*	0/17 (0%)	9/12 (75%)	14/19 (73.7%)	20/21 (95.2%)
Subjects initiating IFN therapy (n/N, %)	4/18 (22%)	10/14 (71%)	14/19 (74%)	21/23 (91%)
Subjects completing 12 weeks IFN therapy (n/N, %)	1/18 (6%)	5/14 (36%)	10/19 (53%)	15/23 (65%)
Subjects who experienced a drug-related AE at any time (n/N, %)	3/18 (17%)	3/14 (21%)	8/19 (42%)	6/23 (26%)
Subjects who WD due to AE at any time (n/N, %)	0/18 (0%)	2/14 (14%)	1/19 (5%)	1/23 (4%)

*Denominator excludes major protocol violators

LB4

A NOVEL CLASS OF AMPHIPATHIC DNA POLYMERS INHIBITS HEPATITIS C VIRUS INFECTION BY BLOCKING VIRAL ENTRY Takuya Matsumura¹, Takanobu Kato¹, Zongyi Hu¹, Jean-Marc Juteau², Andrew Vaillant², Jake T. Liang¹; ¹liver diseases branch, NIDDK, NIH, Bethesda, MD; ²REPLICOR Inc., Laval, QC, Canada

Hepatitis C virus (HCV) gains entry into susceptible cells by interacting with cell surface receptor(s). While several candidate receptors have been identified, the pathway of viral entry remains largely unknown. Viral entry is an attractive target for antiviral development because of the highly conserved mechanism. Recent studies have shown that long (>30 base) phosphorothioate oligonucleotides (PS-ONs) display a sequence-independent antiviral activity against HIV-1. The amphipathic nature of these long PS-ONs targets them to the amphipathic alpha helices of gp41 and inhibits HIV-1 entry by blocking virus-cell fusion. The broad spectrum activities of these long PS-ONs in all families of enveloped viruses, including viruses with type I or II fusion mechanisms suggest that structural similarities existed between type I and type II fusion proteins. The aim of this study was to assess

whether long PS-ONs inhibited HCV infection by blocking viral entry. Huh7.5 cells were infected with the HCV-containing culture medium (HCVcc) and treated with various PS-ONs to assess their inhibitory activity. To further evaluate the antiviral mechanism of action of PS-ONs, viral binding and entry assays with HCV-like particles (HCV-LPs) and HCV pseudovirus (HCVpp), respectively, were also tested. In addition, several PS-ON analogs were tested for their effect on viral replication in the HCV replicon system. PS-ONs with lengths of 40 to 80mer potentially inhibited HCV infection in both the HCVcc and HCVpp systems. These PS-ONs were equally active against HCVpp of various genotypes. The IC50 was in the range of 10-100 nM. The control phosphodiester-ONs and PS-ONs less than 30mer in length did not display any inhibitory effects. Active PS-ONs had no effect on viral replication in the HCV replicon system and binding of HCV-LPs to cells, indicating that the target of inhibition by PS-ONs is at the post-binding, cell entry step. **Conclusion:** The PS-ONs (amphipathic DNA polymers) are a promising new class of antiviral compounds that inhibit HCV fusion and entry. The similar chemical requirements on the PS-ON structure (size and amphipathic character) for antiviral activity in both HIV-1 and HCV suggest that the entry mechanisms of HIV-1 and HCV are similar.

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LB5

ADEFOVIR AND LAMIVUDINE COMBINATION THERAPY IS SUPERIOR TO ADEFOVIR MONOTHERAPY FOR LAMIVUDINE-RESISTANT PATIENTS WITH HBEAG-NEGATIVE CHRONIC HEPATITIS B Pietro Lampertico¹, Alfredo Marzano², Massimo Levrero³, Teresa Santantonio⁴, Vito Di Marco⁵, Maurizia Brunetto⁶, Pietro Andreone⁷, Eoangelista Sagnelli⁸, Stefano Fagioli⁹, Giuseppe Mazzella¹⁰, Giovanni Raimondo¹¹, Giovannibattista Gaeta¹², Antonio Ascione¹³, *Adefovir Study Group on behalf of the AISF¹; ¹Gastroenterology Unit, IRCCS Maggiore Hospital and University of Milan, Milan, Italy; ²Gastroenterology Unit, Ospedale San Giovanni Battista, Molinette Hosp, Torino, Italy; ³Dep. Internal Medicine, University of Rome La Sapienza, Rome, Italy; ⁴Clinic of Infectious Diseases, University of Bari, Policlinico, Bari, Italy; ⁵Istituto di Clinica Medica, University of Palermo, Palermo, Italy; ⁶Gastroenterology and Hepatology Unit, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy; ⁷Dep Internal Medicine, University of Bologna, Bologna, Italy; ⁸Div Infectious Diseases, Azienda Ospedaliera San Sebastiano, Caserta, Italy; ⁹Gastroenterology Unit, Ospedali Riuniti, Bergamo, Italy; ¹⁰Dep. Internal Medicine and Gastroenterology, University of Bologna, Bologna, Italy; ¹¹Dep Internal Medicine, University of Messina, Messina, Italy; ¹²Dep Infectious Diseases, Second University of Napoli, Napoli, Italy; ¹³Hepatology Unit, Azienda Ospedaliera A. Cardarelli, Napoli, Italy*

To assess whether adefovir dipivoxil (ADV) should be "switched" or "added" to lamivudine in lamivudine resistant (LAM-R) patients, we compared the long-term virological response and adefovir resistance (ADV-R) rates of LAM-R, HBeAg-negative patients under ADV+LAM combination or ADV monotherapy. **Material and Methods.** 588 LAM-R patients with HBeAg-negative chronic hepatitis B who started ADV treatment between 2002 and 2004 in 31 Italian centers were enrolled in a prospective cohort study and followed for 24 months, on average. Mean age was 54 years, 85% were men, 49% cirrhotics; 303 (52%) patients switched from LAM to ADV (ADV mono group) while 285 (48%) added ADV to LAM (combo group). HBV-DNA was quantified by sensitive assays (LLQ: 2 or 3 log copies/mL); a virological response was an undetectable HBV-DNA, a virological rebound was a confirmed > 1 log increase of HBV-DNA; ADV-R was confirmed by molecular analysis. **Results.** Baseline demographic, clinical and virological characteristics as well as duration of follow-up were similar between treatment groups. The 6 and 12-month rates of HBV DNA undetectability were 47% and 66% in the ADV mono group and 49% and 64% in the combo group, respectively ($p=ns$). After a median follow-up of 24 months, 67% of the patients in the former group cleared HBV DNA compared to 69% of those in the

latter one ($p=ns$). Residual viremia was similar in incomplete responders from both groups (4.8 vs 4.9 log copies/ml of HBV DNA). By converse, the rates of virological breakthrough were significantly higher in the ADV mono than in the combo group (9% vs 2%, $p<0.001$) and ADV-related signature mutations were identified more frequently in the former than in the latter group (5% vs 0.8%, $p<0.01$). At multivariate analysis, patients treated with ADV monotherapy had higher chances of experiencing a virological rebound ($p<0.001$), indicating that although ADV-LAM combination therapy does not suppress HBV replication more rapidly than ADV monotherapy, it significantly reduces the risk of virological breakthrough and genotypic resistance to ADV. Conclusions. In HBeAg-negative LAM-R patients, ADV should be added to LAM and both drugs should be continued to reduce the risk of ADV-related secondary treatment failure.

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LB6

A PROSPECTIVE, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED TRIAL OF TERLIPRESSIN FOR TYPE 1 HEPATORENAL SYNDROME (HRS) Arun Sanyal¹, Thomas Boyer², Guadalupe Garcia-Tsao³, Frederick Regenstein⁴, Lorenzo Rossaro⁵, Peter Teuber⁶, Study Group Hepatorenal⁶; ¹Internal Medicine, Virginia Commonwealth University, Richmond, VA; ²Internal Medicine, University of Arizona, Tucson, AZ; ³Internal Medicine, Yale, New Haven, CT; ⁴Internal Medicine, Tulane, New Orleans, LA; ⁵Internal Medicine, University of California Davis, Sacramento, CA; ⁶Orphan Therapeutics, Newark, NJ

Background: Type I HRS is characterized by rapidly progressive functional renal failure in subjects with cirrhosis and is associated with a 90 day mortality exceeding 90%. Uncontrolled trials suggest that vasoconstrictor therapy plus albumin improve HRS. However, there are no phase III controlled trials of such agents in HRS. Aims: We report the preliminary analysis of a phase III prospective, randomized, double-blind, placebo-controlled trial of terlipressin, a vasopressin analog, for Type 1 HRS. Methods: Type 1 HRS was defined using the International Ascites club criteria (Hepatology 1996, 23:164-176). Subjects were randomized (1:1) to receive terlipressin (1mg/Q 6h) or placebo I.V. in addition to albumin until creatinine decreased to ≤ 1.5 mg/dl on 2 measurements 48 h apart or for up to 14 days (treatment stopped earlier for treatment failure or transplantation). If after 3 days, creatinine had not improved by $\geq 30\%$ the dose was increased to 2 mg Q 6h. Failure was defined as death, dialysis or failure of creatinine to improve after 7 days. Results: 112 patients were enrolled, 56 Terlipressin (MELD = 33 ± 6.2) and 56 Placebo (MELD = 33 ± 6.4). The primary end-point (patient alive on day 14 with creatinine ≤ 1.5 mg/dl on 2 measurements 48 h apart without relapse of creatinine after the improvement) was reached in 27% of subjects receiving terlipressin and 16% of those getting placebo ($p = 0.059$). There was a significant reduction in serum creatinine in those receiving terlipressin vs. placebo from baseline to day 14: -0.7 vs 0 mg/dl, $p<0.009$. In addition, the commonly used criterion for reversal of HRS in the literature of creatinine of ≤ 1.5 mg/dl on treatment was achieved in 34% (terlipressin) vs. 13% (placebo) ($p = 0.008$). Overall survival and transplant free survival at 60 days were similar, 48% & 48%-terlipressin vs. 48% & 46%-placebo respectively. The incidence of adverse (93% terlipressin vs. 89% placebo) and serious adverse events (66%-terlipressin vs 66%-placebo) was similar in the two groups. Treatment related serious adverse events occurred in 5 patients on terlipressin and 1 on placebo and there were no treatment related deaths. Summary: Using the primary end-point, terlipressin improved outcome of type 1 HRS but this narrowly failed to achieve statistical significance. However, using either improvement in serum creatinine or HRS reversal on treatment, Terlipressin was significantly more effective than Placebo. The overall safety profile of terlipressin was similar to Placebo. Conclusion: Terlipressin is an effective and safe therapy for HRS type 1.

Disclosures:

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LB7

NK LYMPHOCYTES DIRECT CYTOTOXICITY TO CHOLANGIOCYTES AND INJURY OF EXTRAHEPATIC BILE DUCT EPITHELIUM IN EXPERIMENTAL BILIARY ATRESIA Prnavkumar Shivakumar, Gregg Sabla, Andrew Chu, Jorge Bezerra; Gastroenterology, Hepatology & Nutrition, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Hepatic lymphocytes and proinflammatory signals are increased in children with biliary atresia. Based on the role of NK lymphocytes in T cell recruitment and innate immunity, we hypothesized that NK lymphocytes induce injury to bile duct epithelium. To test this hypothesis, we used flow cytometry to quantify CD4+, CD8+, CD19+, NK and NKT lymphocytes, neutrophils and macrophages in microdissected extrahepatic bile ducts from neonatal mice at 3-14 days after rhesus rotavirus (RRV) or saline challenge. NK cells were the most abundant cells in RRV-primed bile ducts, with a 20-fold rise above saline controls at the time of duct obstruction. NK cells exhibited an activated phenotype with a 128-fold increase in CD107a expression and high levels of interferon-gamma. To determine whether this activation directs NK cell killing toward duct epithelium, we performed cytolytic assays with NK cells from livers of mice 7 days after RRV or saline challenge in co-culture with murine cholangiocytes. RRV-primed NK cells induced lysis of 53% of cholangiocytes after 5 hours of culture, while saline-NK cells displayed no cytolytic activity. Induction of the immunologic synapse was demonstrated by increased expression of NKG2D in NK cells and of NK ligands in cholangiocytes (RAET1A-E, H-60 and MULT1), and by the loss of NK cell-induced cytotoxicity when cell-cell contact was prevented in a Transwell experiment. To determine whether NK-dependent cytotoxicity is a key pathogenic mechanism of atresia, we inoculated RRV or saline into neonatal mice, and half the mice in each group underwent NK cell depletion by daily administration of GM1 antibody. While RRV induced duct obstruction and cholestasis within 7 days and death by 14 days in controls, 88% of NK cell-depleted mice survived beyond 15 days. NK cell depletion resulted in milder cholangitis, as shown by a 52% reduction in mononuclear cells in bile ducts by flow cytometry; duct epithelium appeared intact and unobstructed. To investigate the impact of the dual loss of NK and CD8+ cells in biliary atresia, we depleted NK cells in Rag2 mice, which completely prevented duct injury and obstruction and allowed for long-term survival in all mice. In conclusion, NK lymphocytes: 1) are the predominant inflammatory cells in extrahepatic bile ducts during experimental atresia, 2) engage cholangiocytes to promote cytotoxicity, 3) mediate epithelial injury in vivo, and 4) work in synergy with CD8+ lymphocytes to regulate bile duct injury and obstruction. These findings establish a key effector role for NK cells in the onset of biliary injury and point to potential therapeutic approaches to target subsets of lymphocytes in biliary atresia.

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LB8

P53 RESTORATION IN LIVER CARCINOMAS INDUCES CELLULAR SENEESCENCE AND TUMOR CLEARANCE THROUGH AN INNATE IMMUNE RESPONSE Lars Zender¹, Wen Xue¹, Carlos Cordon-Cardo², Scott W. Lowe¹; ¹Cold Spring Harbor Laboratory, Cold Spring Harbor, NY; ²Memorial Sloan Kettering Cancer Center, New York, NY

Although cancer arises from a combination of mutations in oncogenes and tumor suppressor genes, the extent to which tumor suppressor gene loss is required for the maintenance of established tumors is poorly understood. In part, this lack of knowledge is due to the fact that technological approaches to effectively regulate endogenous tumor suppressor gene expression in vivo were missing. Herein we use powerful conditional RNA interfer-