Methods: Three hundred HCV patients and 860 family members were studied. All family members were screened for HCV antibodies by ELISA. Positive cases were examined using Real-Time PCR to confirm the presence of HCV-RNA. Seventy five patients of 300 were treated using SOC treatment. Molecular study of IL-28B gene was done to all patients and their families using PCR and restriction enzyme analysis.

Results: IL-28B gene (rs12979860) polymorphism in patients was 27.43%, 55.43% and 17.14% for C/C, C/T and T/T genotypes respectively, in non infected family members was 37.38%, 44.05% and 18.57% for C/C, C/T and T/T respectively. There was significant increase as regard CC genotype in non-infected family members than patients. Of the treated 75 patients, 36 achieved SVR (48%). Better response to treatment was found in CC genotype (75%) than CT (48%) and TT (28.5%).

Conclusions: CC genotype for IL-28B gene has better response to treatment and may have a protective role against HCV infection as it detected significantly in non infected family members of HCV patients.

Acknowledgement: Project was funded by Science, Technology Development Fund (STDF), Egypt, Grant No. 1687.

P1220

MODELING PREDICTS CLINICALLY MEANINGFUL SVR RATES IN GENOTYPE 1 TREATMENT-EXPERIENCED PATIENTS BASED ON RESULTS IN GENOTYPE 1 TREATMENT-NAIVE PATIENTS TREATED WITH SOFOSBUVIR + PEGINTERFERON + RIBAVIRIN FOR 12 WEEKS

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Background and Aims: In NEUTRINO, 89% of the treatment-naive (TN) patients with HCV genotype (GT) 1 receiving sofosbuvir (SOF)+peginterferon (PEG)+ribavirin (RBV) for 12 weeks achieved an SVR. Treatment-experienced (TE) patients with HCV GT1 were not evaluated. Given this high response rate, exploratory methods were used to predict a potential response rate for TE patients with HCV GT1.

Methods: Three exploratory methods were used to predict the SVR12 rate in GT1 TE patients. Method 1 assumes that in TN patients, approximately 50% will fail PEG+RBV. With SOF+PEG+RBV, 89% responded implying that 39% of the 50% who would have failed PEG+RBV would respond to SOF+PEG+RBV, resulting in a 78% SVR rate (39/50) for SOF+PEG+RBV in GT1 TE patients. Methods 2 and 3 assume that differences in response rates between TN and TE patients receiving telaprevir+ PEG+RBV are similar to relative differences in response rates between TN and TE patients receiving SOF+PEG+RBV. Method 2 uses a difference in response rates to define the relative difference. Method 3 uses a log odds difference.

<table>
<thead>
<tr>
<th>Method</th>
<th>Projected SVR Rate (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method 1 (Additional Benefit)</td>
<td>78% (71, 86)</td>
</tr>
<tr>
<td>Method 2 (Response Rate Difference)</td>
<td>79% (71, 87)</td>
</tr>
<tr>
<td>Method 3 (Log Odds Difference)</td>
<td>84% (76, 90)</td>
</tr>
</tbody>
</table>

Results: All 3 methods predicted that TE patients with HCV GT1 receiving 12 weeks of SOF+PEG+RBV would achieve an SVR12 rate ranging from 78% to 84%. Our analysis also predicted that within the subset of prior null/partial responders receiving 12 weeks of SOF+PEG+RBV, SVR rates would range from 56% to 67%.

Conclusions: These analyses suggest that SOF+PEG+RBV may provide a potential treatment option in TE GT1 patients. Studies are ongoing to evaluate SOF+PEG+RBV in patients who have failed PEG+RBV +/- protease inhibitors.

P1221

PHARMACOKINETIC (PK) DRUG–DRUG INTERACTION BETWEEN SAMATASVIR (IDX719), A PAN-GENOTYPIC NSSA INHIBITOR, AND SIMEPREVIR IN HEALTHY VOLUNTEERS AND HCV-INFECTED SUBJECTS

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Background and Aims: PK drug-drug interaction (DDI) between samatasvir, a pan-genotypic NSSA inhibitor, and simeprevir, an NS3/4A protease inhibitor, was assessed in healthy volunteers and HCV-infected subjects.

Methods: Healthy volunteers (N=32) were randomized equally to receive one of two study drugs for 14 days (150 mg QD for both drugs), with the other drug added on Day 8 and continued for 7 days. PK of the study drugs alone and in combination was evaluated on Days 8 and 14, respectively. Treatment-naïve HCV genotype 1b- or 4-infected subjects (N=60) were randomized equally to receive samatasvir (50, 100 or 150 mg QD) in combination with simeprevir 150 mg QD and ribavirin for 12 weeks as part of the HELIX-1 study. Intensive PK was performed at Day 14 with troughs obtained weekly.

Results: The study drugs were well tolerated in both populations. In healthy subjects, steady-state plasma exposures of samatasvir approximately doubled (mean ratios 1.87 and 2.22 for Cmax and AUC) in the presence of simeprevir. Plasma exposures of simeprevir were increased by 40–50% (mean ratios 1.47 and 1.49 for Cmax and AUC) in the presence of samatasvir. Elimination half-lives of both drugs remained unaffected. Exposures of samatasvir and simeprevir in combination were comparable to previous data. A positive correlation between the plasma PK parameters of samatasvir and simeprevir was observed.

Conclusions: The combination of samatasvir and simeprevir was well tolerated and resulted in increased plasma concentrations for both drugs. The observed safety and PK data support investigating all-oral regimens involving samatasvir and simeprevir.
**POSTERS**

**Methods:** This is a randomized, double-blind, parallel-group study in treatment-naïve subjects with GT1b and 4 chronic HCV infection. Subjects received 50, 100, or 150 mg samatasvir + SMV 150 mg + weight-based ribavirin (RBV) daily for 12 weeks. Subjects received 50, 100, or 150 mg samatasvir + SMV 150mg + weight-based ribavirin (RBV) daily for 12 weeks. Subjects received 50, 100, or 150 mg samatasvir + SMV 150mg + weight-based ribavirin (RBV) daily for 12 weeks. Subjects received 50, 100, or 150 mg samatasvir + SMV 150mg + weight-based ribavirin (RBV) daily for 12 weeks. Subjects received 50, 100, or 150 mg samatasvir + SMV 150mg + weight-based ribavirin (RBV) daily for 12 weeks.

**Results:** 63 subjects randomized: 59% female, 24% African American, 91% GT1b and 8% GT4 HCV infection. Mean baseline HCVRNA was 6.4 log10 IU/mL. On-treatment responses are presented in the table.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>50mg QD Samatasvir (N=20)</th>
<th>100mg QD Samatasvir (N=21)</th>
<th>150mg QD Samatasvir (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCVRNA &lt;LLOQ at Week 4 (RVR), n/N (%)</td>
<td>20/20 (100%)</td>
<td>20/21 (95%)</td>
<td>18/19 (95%)</td>
</tr>
<tr>
<td>HCVRNA &lt;LLOQ at Week 8, n/N (%)</td>
<td>19/20 (95%)</td>
<td>20/21 (95%)</td>
<td>16/19 (84%)</td>
</tr>
<tr>
<td>Median time to HCVRNA &lt;LLOQ, days</td>
<td>15 days</td>
<td>10 days</td>
<td>13 days</td>
</tr>
</tbody>
</table>

LLOQ (lower limit of quantitation) = 25 IU/mL.

**Results:** E2216 was observed to selectively block HCV infectivity of both HCVcc and HCVpp with an IC50 of 6.2uM and 3.3uM respectively.

**Conclusions:** E2216 appears to be a promising drug lead that targets HCV E2 and can be further optimized to help in blocking HCV entry into hepatocytes and prevent the progression of the infection.

**P1224**

**GSK2878175, A POTENT NON-NUCLEOSIDE INHIBITOR OF HCV NS5B WITH PAN-GENOTYPIC ACTIVITY**

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**Background and Aims:** GSK2878175 is a potent inhibitor of HCV replication. Its in vitro characterization as a non-nucleoside NS5B-palm polymerase inhibitor is presented.

**Methods:** Standard replicon assays were used to assess the antiviral activity of GSK2878175. Physical interactions with NS5B were also analyzed.

**Results:** GSK2878175 had EC50 values ranging from 1.0 to 5.7 nM on stable replicon cell lines containing NS5B from genotypes 1–5. Additional patient sequences from genotypes 1–6 were tested by transient transfection for susceptibility to GSK2878175 yielding EC50 values of 0.42–9.65 nM. Resistance selection identified variants at amino acid positions 316 and 365 in genotype 1. These amino acid changes are associated with non-nucleoside inhibitors binding to allosteric site 4, also known as palm site 2, exemplified by HCV-796. Unlike HCV-796, GSK2878175 retains activity against the genotype 1b C316N polymorphism. The binding of GSK2878175 to NS5B site 4 was confirmed by co-crystallization with NS5B and X-ray structural analysis. The kinetics of GSK2878175 binding to NS5B determined a Kd of 70±40 nM and a slow off rate with a half life of 88–161 hours vs 0.6–1.7 hours for HCV-796. GSK2878175 was not cross resistant with other DAA classes and was non-antagonistic in in vitro combination studies with specific DAs. The combination of GSK2878175 with an NS5A inhibitor resulted in a higher genetic barrier to resistance than either agent alone.

**Conclusions:** GSK2878175 inhibits HCV replication with low nM potency against all genotypes. Its antiviral and biochemical profile makes it an attractive candidate for inclusion in a pan-genotypic all oral DAA regimen.

**8D. VIRAL HEPATITIS: HEPATITIS C – CLINICAL (NEW COMPOUNDS, RESISTANCE)**

**P1223**

**E2216 … A PROMISING DRUG LEAD THAT INHIBITS HCV INFECTIVITY THROUGH TARGETING HCV E2**


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**Background and Aims:** E2 glycoprotein plays a significant role in the HCV life cycle, but only crystal structures of short peptides, or epitopes were present until Kong et al. resolved the new HCV E2 core (E2c) crystal structure. We have created a new HCV E2 homology model based on the new E2c crystal structure, selected 3 potential binding sites located near residues critical for HCV entry, and used computer docking to identify a set of ligands that should bind to the sites. We tested the set for E2 binding using surface plasmon resonance and performed inhibition assays of HCV infection. One of these compounds, E2216, inhibited HCV infectivity.

**Methods:** The homology model was created using AS2TS and Smith-Waterman, FASTA, BLAST and PSI-BLAST sequence alignments. Three potential ligand-binding sites were selected and 3 corresponding grid parameter files were created using Autodock 1.5.6 to guide the virtual screening of ~4,000 ligands (NCI,DSII library). Recombinant HCV E2 protein was used to identify 40 virtual screening hits by using Biacore t100. Pseudotyped retroviral particles harboring HCV envelope proteins (HCVpp) of genotype 2a and cell culture-produced HCV particles (HCVcc) based on the JFH1 strain were used in testing the ligands for HCV infectivity inhibition.

**Results:** E2216 was observed to selectively block HCV infectivity of both HCVcc and HCVpp with an IC50 of 6.2uM and 3.3uM respectively.

**Conclusions:** E2216 appears to be a promising drug lead that targets HCV E2 and can be further optimized to help in blocking HCV entry into hepatocytes and prevent the progression of the infection.

**P1225**

**THE S282T VARIANT IS NOT OBSERVED IN TREATMENT-NAÍVE PATIENTS WITH GENOTYPE 1 HCV INFECTION TREATED WITH RIBAVIRIN**

A. Tigges1, E. Zhang1, A. Davis1, J. Spanks1, J. Dorrian1, J. Symons2, D. Bartels1, J. Fry2, D. Smith-Waterman, FASTA, BLAST and PSI-BLAST sequence alignments. Three potential ligand-binding sites were selected and 3 corresponding grid parameter files were created using Autodock 1.5.6 to guide the virtual screening of ~4,000 ligands (NCI,DSII library). Recombinant HCV E2 protein was used to identify 40 virtual screening hits by using Biacore t100. Pseudotyped retroviral particles harboring HCV envelope proteins (HCVpp) of genotype 2a and cell culture-produced HCV particles (HCVcc) based on the JFH1 strain were used in testing the ligands for HCV infectivity inhibition.

**Background and Aims:** VX-135 is a uridine nucleotide analog in development for treatment of HCV. A Phase 2a study in treatment-naïve patients with genotype 1 HCV assessed the safety and antiviral activity of 100 and 200 mg VX-135 with RBV for 12 weeks. A rapid reduction in HCVRNA was observed, with most patients achieving levels below LOQ by Week 2, and no on-treatment viral breakthrough. In the 100- and 200-mg cohorts, 1/10 and 5/10 patients achieved SVR12, respectively. Viral resistance was assessed in patients without SVR. In vitro, the NS5B-S282T variant confers an 89-fold reduction in sensitivity to VX-135, with a replication capacity of 2.8% compared with wild-type virus.