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ABSTRACT 030

Antiviral Activity of Pradefovir Mesylate in Patients with Lamivudine-resistant HBV Infection: 24-week Interim Analysis from a Phase 2 Study

WL Chuang, KS Lee, SG Lim, SG Hwang, M Cho, MY Lai, YC Chao, TT Chang, KH Han, CM Lee, SH Um, JE Yoon, SS Yang, EK Teo, CY Peng, HH Lin, SS Yang, TI Huo, T Nguyen, TV Chen, KQ Hu, Y Xu, A Raney, Z Hong and JZ Sullivan-Bolyai

Kochsung Medical University, Kochsung, Taiwan; 2Yonsei University, Seoul, Korea; 3National University, Singapore; 4Ponchon CHA University, Kyonggi, Korea; 5Pusan National University, Pusan, Korea; 6National Taiwan University, Taipei, Taiwan; 7Tri-Service General Hospital, Taipei, Taiwan; 8National Cheng Kung University, Tainan, Taiwan; 9Kochsung Chang Memorial Hospital, Kochsung Hsien, Taiwan; 10Korea University Medical Center (Anam), Seoul, Korea; 11Korea University Medical Center (Kuro), Seoul, Korea; 12Cathy General Hospital, Taipei, Taiwan; 13Changi General Hospital, Singapore; 14China Medical University Hospital, Taichung, Taiwan; 15Tzu Chi General Hospital, Hualien, Taiwan; 16Taichung Veterans General Hospital, Taichung, Taiwan; 17Taipei Veterans General Hospital, Taipei, Taiwan; 18Research & Education, San Diego, California, USA; 19Chung Shan Medical University Hospital, Taichung, Taiwan; 20University of California Irvine, Orange, California, USA; 21Valeant Research & Development, Costa Mesa, California, USA

RESULTS: 28 patients had evidence of LAM resistant HBV at baseline, 4 genotype B and 24 genotype C. Among PDV treated patients, 2 in the 30 mg group had L180M mutations without detectable YMDD mutations. Three had M204I mutation alone; 2 in the 5 mg and 1 in the 20 mg groups. The remaining 20 patients had an M204I or M204V mutation combined with the L180M mutation. Of these, 4, 3, 7 and 6 patients were in the 5 mg, 10 mg, 20 mg and 30 mg groups, respectively. Two of these, 1 in the 5 mg and 1 in the 10 mg groups also had detectable V173M mutation. In the ADV group, 1 patient had the L180M mutation and 2 had the M204I mutation. Results for antiviral activity are presented in the table, below.

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>PDV 5 mg</th>
<th>PDV 10 mg</th>
<th>PDV 20 mg</th>
<th>PDV 30 mg</th>
<th>ADV 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Patients with LAM resistant HBV</td>
<td>n = 6</td>
<td>n = 3</td>
<td>n = 8</td>
<td>n = 8</td>
<td>n = 3</td>
</tr>
<tr>
<td>% patients with HBV DNA less than 400 copies/mL</td>
<td>17</td>
<td>23</td>
<td>38</td>
<td>36</td>
<td>13</td>
</tr>
<tr>
<td># of Patients without LAM resistant HBV</td>
<td>n = 40</td>
<td>n = 40</td>
<td>n = 40</td>
<td>n = 40</td>
<td>n = 40</td>
</tr>
<tr>
<td>Percent patients with HBV DNA less than 400 copies/mL</td>
<td>17</td>
<td>24</td>
<td>28</td>
<td>35</td>
<td>15</td>
</tr>
</tbody>
</table>

CONCLUSION: Although the number of patients with LMV resistance studied was small, the 24-week interim analysis suggests that both PDV 30 and ADV appear to be equally active against LAM resistant HBV and wildtype HBV.

ABSTRACT 031

Three-dimensional Pharmacophore Modeling of Hindered Nucleoside Analogs (HNAs) as Inhibitors of the Hepatitis C Virus NS5B Polymerase

M Ferrone, S Pridi, M Fermaglia, MS Paneni, A Augst, N Ciliberti, L Buzzon, E Durini, S Venturi, M Manfredini, R Loddo and P La Colla

1Molecular Simulation Engineering (MOSE), Department of Chemical Engineering, University of Trieste, Italy; 2Department of Pharmaceutical Sciences, University of Ferrara, Italy; 3Biotechnology Research Institute (NRC), Montreal, Canada; 4Ambrosialab, University of Ferrara, Italy; 5Department of Biomedical Sciences and Technologies, University of Cagliari, Italy

BACKGROUND: The hepatitis C virus has infected an estimated 1-3% of the world population, exceeding 170 million individuals. Current therapies based on
combinations of pegylated interferons and the broad spectrum antiviral ribavirin are ineffective in a significant proportion of cases, and are associated with the occurrence of severe side effects. A growing patient population is in urgent need for novel therapies that could address a clearly unmet medical need. The HCV NS5B RNA-dependent RNA-polymerase (RdRp) is a central enzyme in the replication of the virus, and has become a target of choice for the screening and design of new inhibitors which, in principle, should interfere with viral replication. Under this perspective, we recently synthesized and evaluated a series of hindered nucleoside analogs (HNA), possessing notable anti-
Flaviviridae activity, as inhibitors of HCV RdRp. Starting from these molecular sets, we developed a 3D chemical feature-based pharmacophore model to be used in the accelerated discovery of novel, more potent hepatitis C virus inhibitors.

METHODS: In this work we designed a molecular modeling strategy using some molecular test sets selected from HNAs as potential HCV polymerase inhibitors. Accordingly, 3D chemical feature-based pharmacophore models were developed for each series of compounds. These simple but highly effective models were then used to predict the anti-Flaviviridae activity of all derivatives previously synthesized in our laboratories, achieving an outstanding agreement between experimental and simulated data. For the most promising compounds, the interactions with the HCV RdRp was further studied, both qualitatively and quantitatively, by detailed molecular modeling techniques carried out in the framework of the Molecular Mechanics/Poisson-Boltzmann Surface Areas (MM/PBSA) computational method.

RESULTS: The developed 3D pharmacophore models allowed to correctly predict the activities for all compounds belonging to the different HNA sets considered. These results demonstrate that the simple models derived in this study can be considered as a useful tool in designing new leads based on HNA scaffolds as anti-Flaviviridae agents. Furthermore, atomistic molecular dynamics simulations allowed clarifying in details the interactions between the most active compounds and their most probable viral target, the HCV RdRp.

CONCLUSIONS: A series of 3D chemical feature-based pharmacophore models were elaborated for different series of hindered nucleoside analogs showing anti-
Flaviviridae activity using a quantitative approach. The models were highly predictive for all compound sets considered. More importantly, the results of these studies, coupled with detailed molecular simulation studies, provided confidence for the utility of the selected chemical feature-based pharmacophore models in the development of new compounds with desired anti-Flaviviridae biological activity by computer virtual screening and characterization.

ABSTRACT 032
Dual Inhibition of HCV and HIV: A Ring-expanded ("Fat") Nucleoside Exhibits Highly Potent In Vitro Inhibitory Activity Against Both Viruses

N Zhang1, P Zhang2, R Narayan2, L Cova2, P Borowski2, V Yedavalli2, K-T Jeang3 and RS Hosmane4

1Laboratory for Drug Design and Synthesis, Department of Chemistry & Biochemistry, University of Maryland, Baltimore County, Baltimore, Maryland USA; 2INSERM U271, Virus des hépatites et pathologies associées, Lyon, France; 3Abteilung für Virologie, Bernhard-Noch-Institut für Tropenmedizin, Hamburg, Germany; 4Laboratory of Molecular Microbiology, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health, Bethesda, Maryland, USA

HCV is a major co-infection in patients infected with HIV, and a number of them ultimately die of end-stage HCV-related complications including liver cirrhosis and hepatocellular carcinoma. Therefore, a drug with dual inhibitory characteristics against both viruses is highly desirable. We report here the synthesis and antiviral activities of a ring-expanded ("fat") nucleoside analogue that inhibits both HCV and HIV in vitro with EC50 values ranging in nanomolar and micromolar concentrations, respectively, with high therapeutic indices against both viruses suggesting little or no toxicity to the host cell lines. The anti-HCV activity was evaluated using two different in vitro quantitative assays employing the subgenomic HCV replicon system in stably transfected human hepatoma BM 4.5 cells as well as the HCV RNA replicon system with a stable luciferase (LUC) reporter. The in vitro anti-HIV activity was determined by assaying the RT (reverse transcriptase) activity in HIV-infected MT-4 cell line treated with and without the inhibitor.