of influenza virus attachment, containing sialooligosaccharide 6-sialyl(*N*-acetyllactosamine) (6′SLN), on the pandemic influenza A (H1N1) virus. The antiviral activity of attachment inhibitor against pandemic influenza virus A/California/07/2009 (H1N1) was examined in the inhibition assay of infectious focus forming in MDCK cells. To characterize efficacy of inhibitors in vivo we have investigated a mouse model, based on measuring the value of 50% respiratory infectious dose for mice. The inhibitor of influenza virus attachment exhibits potent inhibitory activity against pandemic influenza A (H1N1) virus. The value of 50% inhibiting concentration (IC50) of attachment inhibitor obtained in MDCK cells was 0.07 (±0.005) μM. Intranasal administration of attachment inhibitor (2 mg/kg) completely protected mice from influenza virus A/California/07/2009 (H1N1) infection. Low-molecular inhibitor of influenza virus attachment did not negatively interfere with the proliferative and metabolic capacity of cells as determined in MTT assay. The results of this study suggest that low-molecular polyvalent inhibitor of influenza virus attachment represents a potential therapeutic agent for prevention and treatment of the pandemic influenza A (H1N1) virus.

doi:10.1016/j.antiviral.2010.02.400

91

Therapeutic Response Guided Interferon Therapy Among Patients Chronically Infected with Hepatitis C Virus

Abida Raza[1,*], Hafsa Aziz[1], Naseeb Zaman[2], Iqbal Yousuf[3], Faateh Din[4], Shahnaz Murtaza[1], Javed Irfan[1], Mukhtar Muhammad[2]

[1] *Nuclear Medicine, Oncology & Radiotherapy Institute, Islamabad, Pakistan;* [2] *PMAS Arid Agriculture University, Rwp, Pakistan;* [3] *Pakistan Council for Science & Technology, Isb, Pakistan;* [4] *National Institute of Population Studies, Isb, Pakistan*

In Pakistan current standard of care for patients chronically infected with hepatitis C virus is combination therapy with interferon-alpha 2b (IFN-alpha-2b) and ribavirin. Treatment outcomes vary patient to patient and are associated with several multiple factors like genetic predisposition of host and viral genotype. In Pakistan, HCV genotype 3a is most prevalent and a viral response with standard therapeutic regimen (STR) varies and ultimately decides about the sustained virological response (SVR). We performed a prospective study to correlate SVR with rapid virological response (RVR) and early virological response (EVR) among individuals chronically infected with HCV confirmed through ELISA and PCR with primers specific for HCV genotype 3a. A total of 1471 (550 males and 732 females) individuals received 300MU IFN-alpha-2b (thrice a week) and 800–1200 mg ribavirin (adjusted to patient's weight) daily. The RVR, EVR and ETR (end treatment response) values are based on post-treatment HCV RNA determination through real time PCR at weeks 4, 12, and 24. Among 1471 participants 452 (30.7%) did not respond to STR. In this cohort, 637 patients achieved RVR whereas 575 patients had revealed an EVR. Individuals with EVR having higher compliance in their treatment (83% and above) showed an SVR of 68.5%. Group with RVR and higher compliance in their treatment had an SVR of 96%. The data suggests that individuals in compliant with their treatment having higher RVR significantly influence SVR towards better remission. Such individuals can be treated with short duration with standard of care treatment; whereas patients achieving a partial EVR have lower rates of SVR (58%) need prolonged treatment of 48 weeks. There was no gender bias in treatment outcomes but in females EVR was significantly correlated with early normalization of ALT. Our research data strongly suggest importance of RVR and EVR in deciding the treatment outcomes and duration of treatment with INF and ribavirin among individuals chronically infected with HCV.

doi:10.1016/j.antiviral.2010.02.401

92

The NF-KappaB-Inhibitor SC75741 Efficiently Blocks Influenza Virus Propagation *In Vitro* and *In Vivo* Without the Tendency to Induce Resistant Virus Variant

Sarah Reiling[1,*], Karoline Droebner[1], Christina Ehrhardt[2], Eike Hirinus Hrincius[2], Stephan Ludwig[2], Oliver Planz[1]

[1] *Friedrich-Loeffler-Institut, Institute of Immunology, Tübingen, Germany;* [2] *Institute of Molecular Virology (IMV), University of Münster, Münster, Germany*

Influenza remains a formidable foe throughout the world. The appearance of pandemic H1N1 and highly pathogenic avian H5N1 viruses in humans and the emergence of resistant seasonal H1N1 variants against neuraminidase inhibitors highlight the need for new and amply available antiviral drugs. We and others have demonstrated that influenza virus misuses the cellular IKK/NF-kappaB signalling pathway for efficient replication suggesting that this module may be a suitable target for antiviral intervention. Here we show that the novel NF-kappaB inhibitor SC75741 efficiently blocks replication of influenza A and B viruses, including avian and human A/H5N1 isolates in vitro in concentrations that do not affect cell viability or metabolism. In a mouse infection model with highly pathogenic avian influenza viruses A/H5N1 and A/H7N7, we were able to demonstrate reduced clinical symptoms, and survival of SC75741 treated mice. Moreover, influenza virus was reduced in the lung of drug-treated animals. Besides this direct antiviral effect the drug also suppresses H5N1-induced overproduction of cytokines and chemokines in the lung, suggesting that it might prevent hypercytokinemia that is discussed to be associated with pathogenesis after infections with highly pathogenic influenza viruses, such as the A/H5N1 strains. Most importantly the drug did not show any tendency to induce resistant virus variants. Thus, a SC75741-based drug may serve as a broadly active non-toxic anti-influenza agent.

doi:10.1016/j.antiviral.2010.02.402

93

Trypsin Digestion of Hepatitis C Virus NS5B Polymerase Exposes a Hinge at the Active Site

Karen Rigat*, Yi Wang, Thomas W. Hudyma, Min Ding, Xiaofan Zheng, Robert G. Gentles, Brett R. Beno, Min Gao, Susan B. Roberts

Bristol-Myers Squibb, Wallingford, USA

Tryptic protease digestion of the hepatitis C virus RNA-dependent RNA polymerase NS5B exposes the effects of inhibitors, RNA template, RNA template/primer, and NTP binding on enzyme conformation. In the absence of inhibitors or substrates, all regions of NS5B are equally resistant to protease treatment and no definitive cleavage products form. Binding of an inhibitor to the thumb-finger site defined by proline 495 resistance substitutions (P495 site) induces a change in NS5B conformation and the formation of a specific trypsin cleavage product. Edman sequencing of the product revealed the trypsin cleavage site is adjacent to the active site in NS5B. A similar pattern of trypsin cleavage was detected for NS5B in the presence of RNA template, but NS5B in the presence of template/primer or in the presence of high concentrations of NTP was more resistant to trypsin cleavage than