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Humanized Neutralizing Monoclonal Antibody and Cyclosporine Treatment for Motor Unit Number Estimation in West Nile Virus Infected Hamster Model

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West Nile virus-induced neurological disease is well known in infected humans and in documented animal models. In our laboratory we established a functional electro-physiological marker, Motor Unit Number Estimation (MUNE), as a measure of the WNV-induced muscle weakness due to spinal cord pathology in infected hamsters. Based on prior efficacy studies by others, and us, we evaluated a humanized monoclonal antibody MGAWN1 (a.k.a. hE16) and an immunosuppressant and inhibitor of cell death, Cyclosporine A (CsA). We hypothesized that MGAWN1 would reduce viral load and CsA would inhibit cell death to improve MUNE in WNV-infected hamsters. To determine the longest treatment delay for MGAWN1, it was administered once subcutaneously (s.c., 32 mg/kg) either on days, 5, 6, 7 or 9 after s.c. challenge with the genotypically dominant WNV (WN02). MGAWN1 administered on days 5 or 6 were efficacious, whereas treatments on days 7 or 9 were not efficacious. CsA administered i.p. twice daily (16 mg/kg/injection) beginning on day 6 through day 20 post-viral injection significantly improved MUNE when measured on days 13 and 14, compared to values of placebo-treated animals. No statistical improvements were observed on survival, weight change, or disease signs. The reason for this may be that mortality and morbidity are simply less sensitive than the neurological endpoint of MUNE. Either by reducing the viral titer or by inhibiting the cell death, MGAWN1 and CsA, respectively, MUNE values were improved in the hamster model.

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Effect of Acridonoacetic Acid on Production of IL-6 in Influenza-infected Peripheral Blood Lymphocytes

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Background: Respiratory virus infections cause upper airway inflammation which is expressed as signs and symptoms orchestrated by the sequential elaboration of various cytokines. Interleukin-6 (IL-6) is a proinflammatory cytokine with pleiotropic expressions consistent with a primary role in the pathogenesis of local inflammation. IL-6 release in vitro by cell lines was observed to be increased after influenza A virus, rhinovirus, and respiratory syncytial virus infections. The main goal of the present study was to evaluate the stimulating effect of inteferon inducer carboxymethylacridanone (CMA) on production of IL-6 by influenza virus-infected peripheral blood leucocytes (PBLs).

Results: It was shown that incubation with CMA leads to sharp elevation of extracellular IL-6 level 10^3–10^4 times comparing to control values. Short-term exposure of stimulated PBLs to influenza virus with further removal of the virus resulted in a dramatic decrease of IL-6 synthesis to basal level. At the same time, long-term (24–72 h post-infection) inoculation of stimulated PBLs with influenza virus did not effect on IL-6 production and its level remained high.

Conclusion: The ability of influenza virus to decrease IL-6 production in stimulated cells at primary contact should be taken into account when prescribing and using inducers of interferon for prophylaxis of influenza.

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Efficacy of Combinations of Oseltamivir and Peramivir in Treating Influenza a (H1N1) Virus Infections in Cell Culture and in Mice

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Emergence of new pandemic strains of influenza and of drug-resistant viruses has caused the medical community to seriously consider combination chemotherapy of these infections. Toward this end, we evaluated two neuraminidase inhibitors, oseltamivir and peramivir, for activity against an influenza A/NWS/33 (H1N1) virus infections. The cell culture-active form of oseltamivir, oseltamivir carboxylate, was combined with peramivir (each at 0.32–100 μM) to treat infections in MDCK cells, and virus yields were determined after 72 h. The results indicated an additive antiviral response from the combinations as measured by MacSynergy software. A neuraminidase assay was performed with these compounds tested in combination at 0.01–10 nm. Lower combined doses of each inhibitor (0.01–0.1 nm) produced a synergistic response. A study using 10 infected mice/group was conducted using doses of 0.05, 0.1, 0.2 and 0.4 mg/kg/day of oseltamivir (oral) and peramivir (intramuscular) administered for 5 days starting 2 h prior to infection. A narrow zone of additive to synergistic activity was seen, and one other data point suggested antagonism. These specific combinations were repeated using 20 mice per group. The antagonistic data point was not reproducible in the second experiment. Two synergistic combinations were confirmed, however: oseltamivir (0.4 mg/kg/day) combined with peramivir at 0.2 and 0.1 mg/kg/day. Thus, the positive benefits of treatment with oseltamivir carboxylate combined with peramivir in vitro translated into improved benefit to infected mice. We conclude that combining two neuraminidase inhibitors (compounds with the same mode of antiviral action) can lead to survival benefits and should be considered as a treatment approach for humans.

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