The data presented suggests a potential role for synthetic CpG in the treatment of infection caused by these viruses and is an area of work still under investigation.

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Efficacy of Oral CMX-001 Therapy Against Human Herpes Virus-6 Infections in SCID-hu Mice

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Human Herpes Virus type 6 (HHV-6) is an infection in infants or immunocompromised individuals which can lead to neurological sequelae. Childhood exanthema, *roseola infantum*, also known as 6th's disease, is caused by HHV-6B and some infants experience convulsions, encephalitis or encephalopathy. The virus is lymphotropic and capable of replication in SCID-hu thymus liver implants, models previously used for determination of antiviral efficacy against human immunodeficiency virus (HIV) or human cytomegalovirus (HCMV). Using these models, we have evaluated CMX-001 (HDP-cidofovir) against both the GS strain of HHV-6A and the Z29 strain of HHV-6B. Briefly, SCID mice were surgically implanted with fragments of human fetal thymus and liver tissue under the renal capsule. Following engraftment, HHV-6A or 6B was directly inoculated into the graft using approximately 5 $\log_{10}$ of virus. Mice were treated with either vehicle or CMX-001 at 10 mg/kg once daily for 12 days beginning 24 h post infection. Samples were obtained approximately one or two weeks post viral inoculation. Real-time PCR was used to determine genome copy number/g of tissue. Samples from vehicle treated mice on day 6 or 13 had 3.7 $\log_{10}$ copies/g tissue of HHV-6A compared to 2.9 and 2.6 $\log_{10}$ copies/g tissue of HHV-6A in CMX treated mice from day 6 or 13, respectively. Samples from vehicle treated mice on day 7 or 14 had 3.6 or 5.8 $\log_{10}$ copies/g tissue of HHV-6B compared to 2.8 and 3.06 $\log_{10}$ copies/g tissue of HHV-6B in CMX treated mice from day 7 or 14, respectively. This represents a significant reduction in viral replication ($p < 0.001$) by day 14. These results indicate that CMX-001, in addition to having potent activity against CMV in the SCID-hu mouse model, also has excellent activity against HHV-6. The results further suggest that CMX-001 should be evaluated for efficacy in a variety of human herpesvirus infections in the immunocompromised host.

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Efficacy of Delayed Therapy Using Combinations of ST-246 with CMX-001 Against Systemic Cowpox Virus Infections in Mice

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Previous studies have shown that either ST-246 or CMX-001 (HDP-cidofovir) are effective in preventing mortality of mice infected intranasally with cowpox virus (CV) or vaccinia virus (VV). While earlier studies paved the way for each potential antiviral compound to move into Phase I clinical trials, evaluation of efficacy using suboptimal doses of these two agents has not been reported previously. As with most infectious agents, the emergence of drug resistance or intentional genetic manipulation to create drug resistant variants by bioterrorists is possible. An orally available drug combination for treatment of orthopoxvirus infections could alleviate some of these concerns, particularly if delayed treatments are effective. In cell culture the combination of ST-246 and CMX-001 resulted in synergistic efficacy with no increase in toxicity. To determine if this combination would result in enhanced efficacy in an animal model, ST-246 was given once daily at 10, 3 or 1 mg/kg with or without CMX-001 to mice infected with CV. CMX-001 was given similarly once daily at 3, 1 or 0.3 mg/kg. Treatments were initiated 72 h or 6 days post infection with CV. ST-246 was given together with CMX-001 as a once daily oral gavage using 0.2 ml volumes for 5 days. ST-246 alone increased mean day to death (MDD) at 10, 3 or 1 mg/kg, but did not improve survival. CMX-001 alone increased survival at 3 mg/kg when given at +72 h, but only increased mean day to death when delayed for 6 days. When ST-246 was given with CMX-001 at 6 days post infection, protection from mortality was significantly enhanced over single drug therapy. Combinations of various doses of these two compounds did not appear to show any additive toxicity and resulted in a synergistic effect on survival. These results indicate that a combination of these two agents act synergistically in vitro and in vivo and should be considered for use in orthopoxvirus infections in humans.

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