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MSL-109 and DHPG Single and Combination Therapy during HCMV-induced Chorioretinitis in the Rabbit. EC Dunkel*, MD Tolpin**, D Freitas*, Q Zhu*, and D Pavan-Langston*. *Eye Research Institute and Department of Ophthalmology, Harvard Medical School, Boston, MA, 02114 and **The Sandoz Research Institute, East Hanover NJ, 07936.

Human cytomegalovirus strain AD169 was used to establish chorioretinal disease in pigmented rabbits by midvitreal injection of 10^5-10^6 PFU. Animals were randomized into groups and received a single intravenous (IV) injection of 5, 1, or 0.25 mg/kg MSL-109 or placebo therapy 48 hours post inoculation (PI). At 84 hours PI, IV DHPG therapy (10mg/kg/day in two divided doses) was begun. All single-agent MSL-109, DHPG and placebo groups and combination MSL-109 + DHPG groups were evaluated daily by indirect ophthalmoscopy, and chorioretinal cell-sonicates were cultured for HCMV on day 7 or 9 PI. Histopathology was performed on selected eyes from each therapy group. HCMV-induced disease in the 5 and 1 mg/kg single-agent MSL-109-treated rabbits was significantly less severe than placebo and single-agent DHPG treated rabbits on days 4, 5 and 7-9 PI. 0.25 mg/kg MSL-109-treated rabbits demonstrated initial improvement followed by a rebound in HCMV chorioretinal pathology on days 6-9 PI. An additive effect was demonstrated in rabbits treated with a combination of 0.25 or 1mg/kg MSL-109 plus DHPG. Histology of the chorioretina in both single and combination drug treated eyes demonstrated localized, focal retinal pathology; placebo treated eyes demonstrated diffuse retinal pathology. HCMV was recovered from chorioretinas of single and combination therapy eyes by cell-sonicate recovery; no statistically significant differences in viral titers were evident between the active therapy groups. These results confirm previous findings on MSL-109 efficacy and indicate that MSL-109 and DHPG are therapeutically active as single agents and combination agents in the rabbit ocular HCMV model.

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The Successful Treatment of Calves Experimentally Infected with Bovine Rhinotracheitis Virus (BHV-1) by means of (S)-1-(3-Hydroxy-2-phosphonylmethoxypropyl) cytosine (HPMPC) During Acute and Reactivated Infections.

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It was established that HPMPC is active against the bovine herpesvirus-1 in tissue culture at a concentration of 4 μg/ml. An experiment was designed to test the efficacy of a single dose of HPMPC in experimentally infected calves. 11 calves, shown to be free from BHV-1 by serological tests, were infected by means of intranasal instillation. All untreated animals developed clinical signs including fever and ocular and nasal discharges. High titres of virus were recovered from nasal and ocular secretions. An injection of 20 mg/Kg of HPMPC given once on the day before, or day after virus inoculation had a profound affect on clinical signs. The therapeutic dose reduced virus shedding in all sites by several log10. The development of antibody to the infecting virus was different in the treated animals compared to untreated controls. Previous experiments showed that reactivation with virus shedding can be obtained reproducibly by means of dexamethasone. It was of interest that the animals which had been treated during the acute infection showed a reduced and different pattern of virus shedding on reactivation. A therapeutic dose of HPMPC was also able to modify the pattern of virus reactivation in animals which had not been treated during the initial infection. We believe that these findings are particularly important since they demonstrate efficacy of a single dose of the antiviral agent HPMPC against an alpha herpesvirus in its natural host as opposed to a laboratory animal model.