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The Safety, Pharmacokinetics, and Anti-CMV activity of weekly HPMPC in HIV positive patients excreting CMV. W.L. Drew, J.P. Lalezari, E. Glutzer, J. Flaherty, J.C. Martin, P.E. Fisher, H.S. Jaffe, Mount Zion Medical Center of UCSF and Gilead Sciences, Inc., Foster City, California, U.S.A.

(S)-1-[3-Hydroxy-2-(phosphonylmethoxy)propyl]cytosine (HPMPC) is a nucleotide analog with potent *in vitro* and *in vivo* activity against a broad spectrum of herpesviruses. Phosphorylation of HPMPC to its' active intracellular metabolite is independent of virus infection and associated with prolonged antiviral effect. We conducted a phase I/II study of weekly intravenous HPMPC in HIV infected patients with asymptomatic shedding of CMV in urine and semen. Five patients were enrolled at each of four dose levels (0.5, 1.0, 3.0, and 10.0 mg/kg) and treated for four weeks. Nephrotoxicity was dose limiting after two doses at the 10.0 mg/kg level and was generally reversible after stopping therapy. Pharmacokinetic profile was consistent with a three compartment model with a terminal serum half-life of 14 hours. Reduction of CMV titer and/or conversion to negative culture was observed at both the 3.0 and 10.0 mg/kg dose levels. Additional studies are underway to define the appropriate dosing regimen for treatment protocols.

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Efficacy of Foscarnet (PFA) Induction Treatment of Human Cytomegalovirus (HCMV) Retinitis in AIDS Patients: Quantitative Virologic Evaluation in Blood and Aqueous Humor. G. Gerna, F. Baldanti, A. Sarasini, M. Furione, E. Percivalle, M.G. Revello and the Italian Foscarnet Study Group. Virus Laboratory, Institute of Infectious Diseases, University of Pavia, IRCCS Policlinico S. Matteo, 27100 Pavia, Italy.

Main objectives of the study were: i) to determine quantitative levels of HCMV pp65-antigenemia, viremia and viral DNA in polymorphonuclear leukocytes (PMNL) as well as (whenever possible) in aqueous humor from 65 AIDS patients with ophthalmoscopically diagnosed HCMV retinitis; ii) to evaluate the efficacy of PFA induction treatment on clinical progression of retinitis as well as on viral load in PMNL and aqueous humor. Blood and aqueous humor samples were drawn before and after treatment. pp65-antigenemia (G. Gerna et al., J. Clin. Microbiol. 30: 1232-7, 1992), viremia and virus isolation from PMNL (G. Gerna et al., J. Clin. Microbiol. 28: 2681-8, 1990) were determined as reported. Viral DNA was quantified by PCR using an external standard curve with an internal control of amplification which was amplified by the same set of primers as for HCMV DNA. Chemosensitivity assays on viral isolates were performed according to a recently developed method (G. Gerna et al., Antivir. Res. 19:333-45,1992). PFA was randomly administered at a dosage of 60 mg/Kg TID or 90 mg/Kg BID for 21 days. Of 56 pts positive for HCMV in blood (12 by PCR only) prior to induction, 41 (73.2%) became negative by all assays, and 15 (26.8%) showed a sharp drop in antigenemia, viremia and viral DNA after induction treatment. Nine pts (13.9%) were negative for HCMV in blood both before and after treatment. As many as 37/39 (94.9%) patients with low viral load (viremia/antigenemia <100; DNA< 5,000 gen. eq.) prior to treatment became negative by all assays, whereas only 4/17 (23.5%) with high viral load (viremia/antigenemia >100; DNA> 5,000 gen. eq.) became negative after treatment. Chemosensitivity assays performed on 35 HCMV isolates recovered prior or during induction treatment detected no PFA-resistant strain and mean ID_{50}, ID_{90} and ID_{99} (±SD) values were 69.9 ± 28.2, 143.2 ± 38.0, and 216.2 ± 59.2, respectively. Of 13 patients positive for HCMV DNA in aqueous humor prior to induction, 5 became negative, 7 showed a sharp decrease in DNA and one showed persisting low DNA levels after induction. Three patients negative in blood after treatment were still positive for viral DNA in the eye. No clinical progression of HCMV retinitis was assessed in 100% pts. In conclusion, the efficacy of PFA induction treatment is remarkable from both the clinical and virologic standpoint. PCR on aqueous humor is essential for etiologic diagnosis and monitoring of HCMV retinitis treatment in AIDS patients. Adverse effects consisting of electrolyte variations, penile ulcerations (2 pts) and nephrotoxicity (3 pts) were consistently reversible. Partially supported by Min. Sanità, ISS, Prog. Naz. AIDS 1993 and CNR Target Project "Biotecnologie e Biostrumentazione".