164

Controlled Trials of Nucleoside Analogs in Chronic Carriers of Woodchuck Hepatitis Virus. JL Gerin[1], BE Korba[1], P Cote[1], WE Hornbuckle[2] and BC Tennant[2]. [1]Division of Molecular Virology and Immunology, Georgetown Univ., Rockville, MD and [2]College of Veterinary Medicine, Cornell University, Ithaca, NY.

The Eastern woodchuck and its naturally-associated hepadnavirus, WHV (woodchuck hepatitis virus), constitute a relevant model for the study of HBV (hepatitis B virus) infection and virus-associated disease in man, including hepatocellular carcinoma. In several controlled studies, groups of 6 chronic WHV carrier woodchucks were treated with 8 different nucleoside analogs, representing various chemical families, which demonstrated antiviral effects against HBV in the human hepatoblastoma cell line, 2.2.15. Compounds were administered by daily intraperitoneal injections at doses of 0.075 to 30 mg/kg for 1 to 3 months. Each compound had an antiviral effect on WHV and was generally well-tolerated by the animals in most cases as judged by clinical, hematologic, and histologic analyses. The relative antiviral activities of these agents against WHV replication in infected animals will be compared. No changes in the levels of viremia or WHV DNA replication intermediates in the liver [WHV RI] of 4 separate control groups of woodchucks were observed during the study periods. The control groups included both untreated and placebo-treated woodchucks. At the end of the treatment periods, serum WHV DNA levels were depressed 100 to 10,000-fold and WHV RI levels were depressed 3 to 30-fold (relative to pretreatment levels) in at least 5 animals in each of the treated groups. The relative levels of viremia and WHV RI in individual animals were well correlated. Viremia declined more rapidly than WHV RI levels in the treated animals. The average levels of viremia and WHV RI in all the treated groups of animals were similar at the end of the treatment period. Following the termination of treatment, viremia and RI levels returned to pretreatment levels in all treated animals 1 to 3 months post-treatment.

165

Experimental Therapy of Immunodeficiency-Inducing Feline Retroviruses with Phosphonylmethoxyethyl Adenine (PMEA). E.A. Hoover*, M. S. Philpott*, J.P. Ebner*, and N.S. Zeidner* *Department of Pathology, Colorado State University, Fort Collins, Colorado, 80523, USA.

We have evaluated the therapeutic efficacy of 9-(2-phosphonylmethoxyethyl)adenine (PMEA) against two immunodeficiency-inducing retroviruses of cats: the FeLV-FAIDS strain of feline leukemia virus (FeLV) and the Petaluma strain of feline immunodeficiency virus (FIV) using in vitro and in vivo evaluation systems. PMEA inhibited the replication of both FeLV-FAIDS and FIV at concentrations of ≥1.6 μM in feline fibroblast or T lymphocyte systems *in vitro*. *In vivo*, PMEA administered to FeLV-FAIDS-infected cats at doses of ≥6 mg/kg/day during the first 6 weeks after virus exposure prevented both the development of persistent antigenemia and the subsequent induction of FeLV-FAIDS disease after an observation period of ≥ one year. In contrast to placebo treated controls, cats successfully treated with PMEA developed neutralizing antibody and were resistant to subsequent re-challenge with the homologous virulent virus. In comparable studies with FIV, PMEA treatment (3 or 6 mg/kg/day) significantly reduced proviral burden in the treated vs. control animals, as evidenced by substantial reduction in the number of proviral copies detected in cultured blood mononuclear cells as measured by a quantitative polymerase chain reaction (PCR) assay and in significantly lower titers of FIV antibody. Eleven months after the cessation of PMEA therapy, the difference in proviral burden between the treated and non-treated FIV-exposed cats had not changed significantly, suggesting that the initial 7-week course of PMEA treatment resulted in a long-lasting effect on FIV replication. These studies in the feline retrovirus immunodeficiency models, therefore, indicate PMEA to be a potent antiretroviral therapeutic agent.

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