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Development of HSV-2 Type-Specific Antibodies to Glycoprotein B In HSV-2 Seronegative Individuals Following Immunization with a Recombinant gB2/gD2/Adjuvant Vaccine. D. Goade, R. Bell, G.J. Mertz, R. Burke, A.G.M. Langenberg, S. Jenison. University of New Mexico, Albuquerque,NM, USA; Chiron Corporation, Emeryville, CA, USA.

HSV-2 glycoprotein B has previously been shown to include an epitope in the amino proximal region that reacts with human antibodies in a type-specific manner, and an epitope in the carboxy proximal region that cross-reacts with both HSV-1 and HSV-2 antibodies. Recombinant proteins expressed by constructs including the HSV-2 type specific epitope (gB2 SS2) and the cross reactive epitope (gB2 SS1) were used as antigen targets in Western immunoblots to evaluate antibody reactivities induced by an HSV-2 candidate vaccine compared to the antibody reactivity seen in native HSV-2 infection. Serum samples from 22 individuals known to be HSV-2 seronegative by glycoprotein G (gG) Western blot were evaluated for development of gB2 antibody reactivities post immunization with a recombinant HSV-2 glycoprotein (gB2/gD2/adjuvant) vaccine. Of 13 HSV 1-/2- vaccinees, all developed gB2 SS2 and SS1 antibody reactivity post immunization characteristic of those seen in native HSV-2 infection. Of 9 HSV 1+/2- vaccinees, all serum samples were reactive to gB2 SS1 prevaccination and all developed gB2 SS2 antibodies post-immunization. Quantitation of antibody response was performed using serial serum dilutions. A total of 16 post-vaccination serum samples were evaluated, eight each from HSV 1-/2- and HSV 1+/2- vaccinees, and compared to 10 serum samples from HSV 2+ individuals. Antibody titers were equivalent between the groups, although HSV 1+/2- vaccinees exhibited a higher range of antibody response than did HSV 1-/2- vaccinees. Median antibody titers were as follows: HSV 1-/2- vaccinees - 1:12,800 (range 1:6400 to 1:25,600); for HSV 1+/2- vaccinees - 1:25,600 (range 1:12,800 to 1:25,600, reactivity of two serum samples exceeded maximal dilution); and for HSV 2+ individuals - 1:12,800 (range 1:6400 to 1:25,600). These findings support previous studies using virus neutralization assays indicating that the recombinant gB2/gD2/adjuvant vaccine induces an antibody response equivalent to those seen in native infection. Development of seropositivity to gB2 SS2 may also serve as a simple assay post-vaccination to assess response.

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Preclinical Safety Assessment of Valtrex* (Valaciclovir, VACV) the L-valyl Ester of Acyclovir (ACV). GM Szczech, P de Miranda, Burroughs Wellcome Co., Research Triangle Park, North Carolina, USA

VACV is an ACV ester for the treatment of herpes zoster and other herpesvirus infections. Given orally VACV is rapidly and extensively converted to ACV and the essential amino acid, L-valine with no other intermediary metabolites. VACV enhances the bioavailability of ACV in a range of animal species and man by two- to five-fold. Three-month studies in CD rats (50, 150, 300 mg/kg/day) and cynomolgus monkeys (200, 400, 600 mg/kg/day) identified the kidney as the only organ demonstrating effects from incremental dosing as expected from studies with ACV. Precipitation of ACV in kidney tubules occurred in both species at the mid and high doses. There were no other signs of toxicity except for minimal, reversible effects on cell maturation in high-dose rats with marked kidney obstruction (AUC 196 μg/ml.h and C_{max} 70 μg/ml for ACV). In 1-year studies there was reversible kidney obstruction in high-dose rats (30, 60, 120 mg/kg/day) but no toxicity in monkeys (125, 250, 500 mg/kg/day). Fertility was normal in rats (50, 100, 200 mg/kg/day). VACV was not teratogenic in rats (400 mg/kg; C_{max} 50 μg/ml ACV) or rabbits (400 mg/kg; C_{max} 34 μg/ml ACV). A peri-/postnatal study was negative in rats. With the exception of effects earlier documented for ACV, VACV was negative in five mutagenicity studies. Rat and mouse carcinogenesis bioassays were negative. The preclinical safety profile established for VACV mimics that established earlier for ACV.