128

Efficacy of BMS-180194 against Opportunistic Cytomegalovirus Infection in Immunocompromised Mice.
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The new antiviral nucleoside, BMS-180194 (SQ 34,514, {R}-BHCG),{(1R-1α,2β,3α)-2-amino-9-[2,3-bis(hydroxymethyl) cyclobutyl]-6H-purin-6-one}, the active R-isomer of racemic cyclobutyl-G, has been shown to be effective in treatment of herpesvirus and murine cytomegalovirus (MCMV)infections in mice. In the present study BMS-180194 was evaluated for effectiveness in a MCMV superinfection in immunocompromised C57BL/6 mice. The immunosuppression was induced by the LP-BM5 murine retrovirus complex resulting in a splenomegaly and generalized lymphadenopathy within 8 to 12 week post-virus inoculation. Between 12-17 weeks post-infection, when splenocytes no longer responded to mitogen stimulation, mice were superinfected intraperitoneally (ip) with MCMV. The drug was administered ip and by oral gavage for the next five days starting 4-6 hr post-MCMV challenge. BMS-180194 was active in this acute MCMV infection with efficacy comparable to ganciclovir (Cytovene or DHPG). These results suggest that BMS-180194 may be of value for treatment of opportunistic CMV infections in immunocompromised patients.

129

A Phase I/IIA Study of a Human Monoclonal Anti-Cytomegalovirus Antibody in Patients with AIDS. R. B. Pollard*, M.A. Nokta*, P. Pappas**, M. Holloway**, M. J. Borucki*, D. L. Wood***, A. M. Zitelli***, M. D. Tolpin***, P. I. Nadler***, and R. J. Whitley**. *University of Texas Medical Branch, Galveston, TX, **University of Alabama, Birmingham, AL, and ***Sandoz Research Institute, East Hanover, NJ

A dose escalating phase I/IIA trial of a human monoclonal anti-cytomegalovirus antibody (MSL-109) was conducted in patients with AIDS without clinical CMV disease but with positive urine and/or buffy coat CMV. Careful toxicity monitoring, pharmacokinetics, and quantitative urine virus cultures were performed. Cohorts of 4 patients each received either MSL-109 (3 patients) or Sandoglobulin (1 patient, 300 mg/kg)) as a control every two weeks for 24 weeks. A total of 28 patients have been entered with 21 receiving MSL-109 and 7 receiving Sandoglobulin. The dosages of MSL-109 utilized included 0.125 mg/kg (4 patients), 0.5 mg/kg (3 patients), 1.0 mg/kg (11 patients), and 2.0 mg/kg (3 patients). No side effects were detected. Three patients expired of unrelated causes while on study medication. One patient developed peripheral retinitis at 4 months, but completed the protocol and 4 patients developed sight threatening retinitis requiring ganciclovir. At 0.125 mg/kg, mean trough serum value of MSL-109 was 1.2 ug/ml, over 2 x the mean ED_{50} against human CMV (approximately 0.5 ug/ml) whereas mean peak level was 3.3 ug/ml, about 6 fold the ED_{50}. At 0.5 mg/kg the mean trough (3.1 ug/ml) and peak (8.7 ug/ml) levels were 6 and 17 x the ED_{50}. At 1.0 mg/kg the mean trough (8.5 ug/ml) and peak (24.2 ug/ml) were approximately 17 and 48 x the ED_{50}, respectively. Evaluation of the influence of MSL-109 on urine CMV shedding is being performed. In summary, MSL-109 was well tolerated and produced trough and peak serum concentrations which greatly exceed the *in vitro* sensitivity of CMV at the higher dosages administered.