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Human Monoclonal Anti Cytomegalovirus (CMV) Antibody (MSL-109): Enhancement of In Vitro Ganciclovir Induced Inhibition of CMV Replication.

M.A. Nokta*, M.D. Tolpin**, P.I. Nadler** and R.B. Pollard*. *Division of Infectious Diseases, The University of Texas Medical Branch, Galveston, Texas, and **Sandoz Research Institute, East Hanover, New Jersey, USA.

Human CMV causes a number of diseases, that tend to be life threatening in immune compromised patients, particularly those with AIDS. Ganciclovir, the drug of choice for management of CMV disease, is not without hazards and has a narrow margin of safety. In this report the effects of a human IgG_1 neutralizing monoclonal antibody MSL-109 (Sandoz Pharmaceuticals) on CMV replication was examined both alone or in combination with Ganciclovir. Human embryonic lung fibroblasts were infected with CMV strain AD169 with a multiplicity of infection of 3 plaque forming units/cell for 1 hour. Prior to infection the virus was neutralized for 30 minutes at 37°C with serial dilutions of the MSL-109 Ab (0.1-3.0 ug/ml). Dilutions of Ganciclovir (0.3 to 30 uM) were added to CMV infected cells that had been either previously neutralized or not. Five days after infection CMV replication was determined by DNA/DNA probe hybridization using the Hyberwix system. The ED_{50} for MSL-109 was 0.5 ug/ml and that for Ganciclovir was 2.4 uM/ml. Doses of 1 ug/ml of MSL-109 enhanced the Ganciclovir (3 uM, 10 uM and 30 uM) mediated inhibition of CMV replication from 59, 91.7 and 96.2% to 90, 99.2 and 99.5% respectively. In an ongoing Phase I/IIA study, peak and trough MSL-109 serum levels of approximately 15 and 4 ug/ml respectively have been attained in AIDS patients receiving 0.5 mg/kg of MSL-109 every 2 weeks without noticeable side effects. Further dosage escalation is ongoing. In conclusion, the MSL-109 enhanced the Ganciclovir induced antiviral effect in a dose dependent manner, suggesting that the combination of MSL-109 and Ganciclovir may be clinically useful in the treatment of CMV disease.

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In Vitro Neutralization of Cytomegalovirus (CMV) Strains by a Human Monoclonal Antibody, MSL-109.

F. Lakeman, Ph.D.*, C. Blevins, B.S.*, R. Whitley, M.D.* and M. Tolpin, M.D.,** *University of Alabama at Birmingham, Birmingham, AL and **Sandoz Research Institute, East Hanover, NJ.

MSL-109 (Sandoz Pharmaceuticals Corporation) is a human anti-CMV monoclonal antibody (Mab) directed to a conformational epitope of the envelope glycoprotein gH. We have utilized a three day neutralization assay to determine in vitro activity of MSL-109 against a variety of clinical and laboratory strains of CMV. CMV isolates were obtained from patients with AIDS, congenital infections and from day care centers; and in addition, DHPG resistant clinical and laboratory strains were analyzed. The assay employed virus mixed with dilutions of antibody and incubated for 1 hour at 37°C followed by centrifugal inoculation into duplicate shell vials containing human fibroblasts. After three days, infected monolayers were incubated with murine Mab, P-63(specific for the immediate-early viral protein, pp-72). After washing, FITC-conjugated anti-mouse antibody was added, and positive nuclei were counted. Effective dose (ED) was calculated using Probit Analysis. The laboratory strain Towne and an isolate from a day care center had the lowest ED/50, 0.1 μg/ml. The highest ED/50 obtained to date (1.12 μg/ml) was for 759-R, a DHPG resistant AD-169 mutant. The ED/90 values ranged from 0.122-4.45 μg/ml. Peak and trough serum MSL-109 levels of approximately 15 and 4 μg/ml respectively have been achieved in ongoing Phase I/IIA clinical trials in AIDS patients receiving 0.5 mg/kg of MSL-109 IV every two weeks. These in vitro results suggest that MSL-109 may be an effective anti-viral for prophylaxis and treatment of patients with CMV infections.