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Efficacy of (*S*)-1-(3-Hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC) in the Treatment of Lethal Vaccinia Virus Infection in Mice with Severe Combined Immune Deficiency (SCID)

J. Neyts and E. De Clercq
Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium

Recombinant vaccinia virus (VV) preparations engineered so as to express HIV genes are attractive HIV vaccine candidates. Although VV vaccination is safe in immunocompetent persons, it may lead to serious complications in immunocompromised patients, thus prompting treatment for the complicating VV infection. We have now evaluated the efficacy of HPMPC in the treatment of VV infection in an animal model that mimics the VV-associated disease progression in immunocompromised patients. SCID mice were inoculated intravenously with 4 x 10^3 PFU of VV, they developed tail lesions, became sick at about 8 days post infection (p.i.) and died at 12 days p.i. Extensive virus replication was observed in the brain, spleen, lungs, pancreas, liver and kidneys. When HPMPC was administered subcutaneously at doses of 1, 5 or 20 mg/kg/day for 5 consecutive days starting on the day of infection, VV-associated death was significantly delayed [mean day of death (MDD): 17.6, 30.0 and 31.4, respectively, as compared to 12.6 for the untreated mice]. Even when HPMPC was administered as early as 7 days before infection (as a single dose of 100 mg/kg) or as late as 6 days after infection (at 25 mg/kg/day on days 6, 7 and 8 p.i.), the compound significantly delayed VV-associated death (MDD: 18.8 and 19.6, respectively). SCID mice which had been treated twice a week with HPMPC at a dose of 20 mg/kg survived for 130 days p.i. HPMPC suppressed VV replication in the tissues (i.e. lungs, kidneys, brain) of the VV-infected SCID mice.

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Protective Activity of Lipid A Analogue GLA-60 Against Murine Cytomegalovirus Infection in Mice

S. Ikeda[1,2], J. Neyts[1], M. Matsuura[3], M. Kiso[4], A. Hasegawa[4], C. Nishimura[2] and E. De Clercq[1]
[1]Rega Institute for Medical Research, Minderbroedersstraat 10, B-3000 Leuven, Belgium, [2]School of Pharmaceutical Sciences, Kitasato University, Tokyo 108, Japan, [3]Jichi Medical School, Yakushiji, Minamikawachi, Tochigi 329-04, Japan, and [4]Faculty of Agriculture, University of Gifu, Gifu 501-11, Japan

A chemically synthesized lipid A subunit analogue, GLA-60 (2-deoxy-4-O-phosphono-2-[(3R)-3-hydroxytetradecanamido]-3-O-[(3R)-3-tetradecanoyloxytetradecanoyl]-D-glucose), has many of the activities of endotoxins but little, if any, toxicity. We investigated the protective activity of GLA-60 against murine cytomegalovirus (MCMV) infection in NMRI mice. Intraperitoneal administration of GLA-60 at 1 day before MCMV infection at doses of 1, 10 or 100 μg per mouse significantly reduced mortality. GLA-60 stimulated peritoneal natural killer (NK) cell and macrophage activities, and these activities were abolished by *in vitro* treatment with anti-asialo GM_1 antibody and anti-Mac_1 antibody, respectively. GLA-60 proved also protective against MCMV infection in mice in which either NK cells or macrophages were depleted by *in vivo* treatment with anti-asialo GM_1 or anti-Mac_1 antibody. The anti-MCMV activity of GLA-60 can at least partially be attributed to activation of NK cells and macrophages.