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Rift Valley Fever Virus Infected Rhesus as a Model for Drug Evaluation: Comparison of Prophylaxis with Ribavirin or Placebo.

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Rift Valley Fever (RVF) virus, found throughout sub-Saharan Africa, causes serious and occasionally fatal infections in man. Ribavirin pharmacokinetics in man can be modeled appropriately only in primates. Rhesus monkeys challenged with Rift Valley fever virus provide a model that mimics the spectrum of disease in man, including the severe hepatic form. Placebo treatment of 8 animals resulted in 3 with severe disease and 1 death (mean peak ALT =2448 U/L); 4 with moderate disease (mean peak ALT= 869 U/L) and 1 with mild disease (ALT=229 U/L). Peak viremia was equivalent in all groups, but viremia duration correlated with disease severity. Ribavirin treatment of 8 animals (50 mg/kg loading dose followed by 10 mg/kg tid, days -1 to +7, IM) significantly lowered mean peak viremia (placebo=6.2 ± 0.5 $\log_{10}$ pfu; ribavirin=2.3 ± 2.0 $\log_{10}$ pfu , $p<0.001$) and decreased mean liver damage (ALT placebo=1108 ± 929; ribavirin=108 ± 31, $p<0.001$) compared to sham-treated control monkeys. Petechiae occurred in 6 of 8 placebo-treated animals, with hemorrhage and death in 1 animal. Platelet counts fell in placebo-treated animals, but increased over pre-treatment values in ribavirin-treated animals. All placebo-treated animals developed clinical disease. Treatment with ribavirin resulted in complete suppression of clinical disease. All surviving monkeys developed neutralizing antibody titers. This model will allow determination of the minimum effective prophylactic dose and comparison of ribavirin analogues.

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Quantitative Measurement of Serum Neopterin in Acute Sandfly Fever Virus (Sicilian) Infection in Medical Research Volunteer Subjects J.I. Smith, T.P. Monath, F.J. Malinoski, D.C. Hack, M. Kende, J.W. Huggins, M. Turell, J. Ortaldo, R.H. Kenyon, T. Ksiazek, J. Morrill, P. Gibbs and K. Womble, Medical, Virology, Disease Assessment and Biometrics Divisions, U.S. Army Medical Research Institute of Infectious Diseases, Frederick, MD 21701-5011.

Sandfly fever is a self-limited, febrile viral illness caused by Sandfly fever virus, belonging to the family Bunyaviridae, genus Phlebovirus; is transmitted by insects of the genus Phlebotomus; and occurs in Africa, Europe and Asia. Humans serve as viremic vertebrate hosts in a human-Phlebotomus-human cycle. Sandfly fever virus infection in humans has a well-defined, very predictable, acute clinical course which is self-limited and has no mortality or sequelae. Neopterin is a stable, soluble, quantifiable metabolite marker of the activation of the T-lymphocyte/macrophage system. It is released from macrophages when stimulated by T-lymphocyte interferon-gamma. We studied serum Neopterin levels in eleven (11) Sandfly fever virus-infected medical research volunteers (MRV) subjects to better understand the kinetic characteristics of cellular immunity during infection. Neopterin concentration, expressed in nMOL/liter, were measured by radioimmunoassay in serial serum samples obtained at day 0 through day 13 of hospitalization. All MRV subjects developed a four to eight times increase in serum Neopterin levels from a baseline level of 4-6 nMOL/liter, progressing to peak levels 16-51 nMOL/liter occurring at day 4-6 of the disease process. All subjects' serum Neopterin levels returned to baseline by day 11 of the disease process. In conclusion, serum Neopterin measurements may prove useful in the study of patients with virus infections, such as Sandfly fever viral infections, and as a marker of the kinetics of T-cell activation during infection and treatment.