79

A TAT Inhibitor (Ro 24-7429): The Single-dose Study in Humans. P.S. Lietman, M.D., Ph.D, R. Ginsberg, M.D., L. Lewis, M.B.B.Ch., M.-C. Hsu, Ph.D., J. Massarella, Ph.D., M. Molle, RPH,M.A., L. Nerhood, R.N., B. Petty, M.D., S. Reele, M.D., W. Soo, M.D., Ph.D., and S. Tam, Ph.D. The Johns Hopkins University School of Medicine, Division of Clinical Pharmacology, Baltimore, MD and Hoffmann-LaRoche, Nutley, NJ.

Ro 24-7429, a member of the benzodiazepine family, has been shown by Dr. Ming-Chu Hsu and her colleagues to inhibit the TAT function of the human immunodeficiency virus (HIV) in in vitro assays and to inhibit the replication of the HIV in both acutely and chronically infected cells in culture. This "first-time-in-man" study was a single-dose pharmacokinetic study, conducted at oral doses of 60 mg and 200 mg in asymptomatic or mildly symptomatic HIV-infected patients. The purpose of this initial study was to provide preliminary human pharmacokinetic data for the selection of a rational dosing regimen for a multiple-dose, dose-ranging study. In addition to pharmacokinetics, tolerance to these single doses of 60 mg and 200 mg was carefully assessed. Adverse events in the four patients who received 60 mg were classified as mild, only possibly related to the drug, transient and non-specific. In the five patients who received 200 mg of the drug, a mild adverse event possibly related to drug was seen in each of two patients. One patient experienced three adverse events of moderate severity and one of mild severity, each of which was categorized as only possibly related to the drug. Two patients had no adverse events. Preliminary pharmacokinetic data derived from the five subjects who received 200 mg of the drug revealed maximum serum concentrations ranging from 1.21 ug/ml to 2.66 ug/ml and occurring 1 hour after oral dosing. The $t_{1/2}$ of the drug was calculated to be about 4 hours.

80

Bone Marrow Stimulatory Cytokines Modulate the Anti-HIV Activity of Nucleoside Analogues in Cultures of Monocyte/Macrophages.

C.F. Perno*, A. Foli§, Z. Hao§, D.A. Cooney§, D.G. Johns§, S. Broder§, R. Calio'*, R. Yarchoan§

§National Cancer Institute, Bethesda, MD, USA, and *University of Rome "Tor Vergata", Italy.

We have studied the ability of granulocyte-macrophage colony stimulating factor (GM-CSF), macrophage-CSF (M-CSF), granulocyte-CSF (G-CSF), and erythropoietin (Epo), to modulate the antiviral activity and the intracellular metabolism of nucleoside analogues in monocyte/macrophages (M/M), cells that play a crucial role in the development of HIV-related disease. GM-CSF and M-CSF substantially increased viral replication in M/M, while G-CSF and Epo had no effect. GM-CSF also enhanced the anti-HIV activity of AZT. For example, 0.01 uM AZT afforded 35% HIV inhibition in control M/M; this increased to >98% inhibition in M/M exposed to GM-CSF. By contrast, the HIV activity of AZT was not increased in M/M exposed to M-CSF, G-CSF, or Epo. Both GM-CSF and M-CSF decreased slightly the antiviral activity of ddC or ddI. Even so, >98% inhibition of HIV replication in GM-CSF- or M-CSF-treated M/M was achieved with 0.1 uM ddC or 10 uM ddI, drug concentrations well below the toxic in M/M, and achievable in patients. Neither G-CSF nor Epo induced any significant modulation of antiviral activity of dideoxynucleosides. We evaluated the metabolic fate of AZT, ddC and ddI in cytokine-exposed M/M. AZT-triphosphate (AZT-TP) levels were increased >4 fold in GM-CSF-exposed M/M compared with controls. In contrast, M-CSF did not induce changes in AZT-TP levels. Enhancement of ddC-TP was increased in GM-CSF- or M-CSF-treated M/M with respect to control M/M. It is possible that a failure to observe an increase in anti-HIV activity was due to a parallel increase in deoxycytidine-TP (which competes at the level of reverse transcriptase). Studies are currently undergoing to further evaluate the levels of endogenous 2'-deoxynucleotide pools and of nucleoside kinases involved in the activation of these drugs. In conclusion, cytokines can modulate the metabolism and activity of anti-HIV drugs.