Oral Session VI

Pharmacology and Animal Models

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Preclinical Development of Recombinant Soluble T4 (sT4) P.J. Bugelski, K-L. L. Fong, H.A. Solleveld, A. Truneh, T.K. Hart, J.L. Perri, R. Kirsh and D.G. Morgan. SmithKline Beecham Pharmaceuticals Philadelphia, PA USA

Human immunodeficiency virus (HIV) is believed to be the cause of the acquired immunodeficiency disease (AIDS). Infection by HIV is initiated by binding of the virus to CD4 (T4) on the surface of susceptible cells. sT4 has been shown to inhibit infectivity and HIV-mediated syncytia formation in vitro and is undergoing clinical trials in AIDS. To facilitate these trials, we conducted toxicity and pharmacokinetic studies in rats and cynomolgus macaques and gamma scintigraphy studies in rats. sT4 was administered by i.v. bolus injection. These studies showed that sT4 has a short biological half life; the majority being eliminated during the alpha elimination phase. Over 75% of the clearance of sT4 is via the kidney. The studies revealed that the principal toxicity of sT4 was tubular cast nephropathy. Kidney lesions were observed in rats at or above 200 mg/kg/day and in monkeys at or above 40 mg/kg/day. These doses are high multiples of the therapeutic dose. The lesions were characterized by proteinaceous casts in distal convoluted tubules and collecting ducts, associated with giant cell formation and PMNs. An interstitial inflammatory cell infiltrate was associated with the affected tubules. The lesions are very similar to those observed in some patients with multiple myeloma and in experimental Bence Jones protein nephropathy. There were no other significant toxic effects identified in rats or monkeys. The studies in monkeys revealed no evidence of immunosuppression as assessed by lectin mediated blastogenesis and mixed leukocyte reactions. There were also no changes in leukocyte subsets and no effect on delayed type hypersensitivity. An IgG response (anti-sT4 antibodies) was found, indicating that sT4 is immunogenic in both rats and monkeys.