Interferons: In Vivo Effects

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The pharmacological effects of Interferons have been studied mostly with human Leucocyte Interferons. They have a short half-life in blood whether given intramuscularly or subcutan-eously or Intravenously. Intramuscular injections result in peak blood levels after 2-4hours, lasting for 4-6 hours. With a dose of 2x10s IU/kg body weight, 100 U of Interferon activity/ ml of Plasma are maintained for 12 hours (Jordon et al., 1974; Arvin et al., 1976; Grecnberg et al., 1976). Human Leucocyte Interferon preparations with specific activity of 10^6 IU/mg protein (purity 0.Interferon protein) are well tolerated, what ever the route of administration. Side effects are dose related febrile responses; usually these are more marked with the initial injections. With daily doses >1.7xl0^5 IU/kg body weight, transient myalgia, chills and fever have been reported, also fatigue and malaise (Jordon et al., 1974; Arvin et al., 1976; Greenberg et al., 1976; Gutterman et al., 1981). Preparation with greater purity (>_10^7 IU/mg protein 1%-10% Interferon Protein) shows significant reduction in the severity of their adverse reactions and have allowed daily administration of 5xl05 IU/kg body weight (Gutterman et al., 1981; Weimer et al., 1978). However at higher doses other effects are observed which include leu-copenia, thrombocytopenia, hair loss and Diarrhea (Gutterman et al., 1981).

Antiviral effects of Interferons were reported initially in early sixties, where Interferon produced by cultured monkey cells inhibited "takes" in Volunteers vaccinated by small pox (Scientific Committee on Interferon, 1962). Vaccinia! Keratitis was successfully treated (Jones et al., 1962) and later human Interferon was successfully used topically against myxoviruses and Herpes simplex (Merigan et al., 1978; Sandmacher et al., 1976). Now there is evidence for systemic Interferon mediated protection against viral infections. Cancer patients receiving interferon as experimental antitumour therapy are protected from Viral infections (Strander et al., 1973; Ahstrom et al., 1974; Strander et al., 1976). For antiviral therapy, systemic administration of Interferon has been tried so far in chronic active hepatitis B and Herpes Zoster in adults and Variscella and Cytomegalovirus in children. Chronic active hepatitis has been selected for trials because several viral markers can be quantitated in patients sera. In one trial (Greenberg et al., 1976) where patients had circulating virus markers for 6 consecutive months, injections of Interferon elicited a dose related response. If given for 10 days the effects were transient while prolonged treatment showed longer lasting effects. In another trial early intensive high dose therapy (>_10^7 U daily) has resulted in suppression of all Virus markers and in progressive improvement in liver function (Merigan and Robinson, 1978). Controlled trials have been carried out with Interferon in cancer patients with Herpes Zoster. In these patients hepatic neuralgia subsided faster, cutaneous dissemination of lesions was lessened, visceral complications and the resulting mortality in patients was reduced (Merigan et al., 1978). In the new born Cytomegalovirus infections have been treated experimentally with Interferon (Arvin et al., 1976; O'Reilly et al., 1976) and congenital CMV infection can be controlled by them (Merigan et al., 1980). Furthermore CMV is of great importance in transp lantations. Renal transplant patients often succumb to CMV induced Hepatitis, pneumonitis or mononucleosis. Also CMV induces immunosuppression and leukopenia which may result in bacterial and fungal infections. In renal transplant patients treated with Leucocyte Interferon, incidence of Virus excretion and viremia with CMV, Herpes Simplex and Epstein Bar Viresus was significantly reduced (Cheesman et al., 1979).

Majority of the studies ot systemic anti-tumour activity of Interferons have been clone with human leucocyte Interferon. It is presently being tested topically (Ikic et al., 1975) and systemically (Krim et al., 1980) against several human tumours. These trials are in various centres with Interferon from

different sources but comparable titre (10^6-10^7 IU/ml) and specific-activity (10^5-10^6 IU/mg protein). The first trial with Interferon in cancer patients was started by Strander in 1972 on highly malignant tumours of the bone. Here treatment with human Leucocyte interferon starts immediately upon diagnosis, prior to surgery, with $3x10^6$U im/day and continues for 1 month. The same dose is then given 3 times weekly for 17 additional months and then treatment is stopped. Strander has reported that 5 of 10 Interferon treated patients have remained alive and disease free after five years (Krim et al., 1980). Interferon trials have been carried out in cancer patients with Laryngeal and Bladder papilloma. Patients with recurrent Laryngeal papilloma were treated with $3x10^6$U Interferon im, one, two or three times a week with no other treatment. In all patients complete regression occurred gradually over a period of several months (Krim et al., 1980). In patients with Bladder Papilloma, with doses of $4xl0^6$U im 3-7 times weekly, complete regression was observed after 2-17 months of treatment (Krim et al., 1980). Several groups have under-taken clinical trials in Multiple Myeloma. In one-study patients receive $3xl0^6$U Interferon daily and in another study by Gutterman two deses have been used $3xl0^6$U or $9xl0^6$U daily. Positive response was observed in both studies with complete remission in some patients (Gutterman et al., 1981; Gutterman et al., 1979). Small number of patients with acute and chronic Leukaemias have received Interferon therapy with suggestive evidence of response (Hill et al., 1979; Gutterman et al., 1970). Little work has been done on the effect of Interferons on solid Tumours. The first study has been by Gutterman on patients with breast Cancer. Two doses were used $3xl0^6$U daily or $9xl0^6$U daily. Patients studied had superficial metastases which allowed measurement of Tumour size. Regression was observed in soft tissues, in bone metastases and in marrow infiltration and Carcinoembryonic antigen levels decreased in responding patients (Gutterman et al., 1979; Borden et al., 1980).

These early studies using highly impure preparations of Interferons give evidence of their being agents for anti-viral anti-tumour therapy. The present methods of production arc adequate to support substantial clinical studies, however for efficient and economical production of Human interferons one has to exploit techniques of recombinant DNA technology (Taniguechi et al., 1969; Negata et al., 1980;. With these techniques the wide spread use of interferons therapy under economically feasible conditions is possible in future.

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