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Interferons as antivirals in man

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Interferons have now been used in both prophylaxis and treatment of a number of human viral infections. The major action has been as a prophylactic for sites within the body that are not yet involved by disease. Such a prophylactic effect can be obtained early in the treatment of acute viral infection or even during chronic viral disease. Both local and systemic prophylaxis have been achieved with regard to both respiratory and herpesviral illness. In addition, Dane particle suppression can be achieved consistently with dosages of 10^6 units or greater daily to patients with chronic hepatitis B virus infection. In certain cases with prolonged therapy there can be permanent eradication. With leucocyte-derived material of approximately 10^6 or 10^7 units per milligram protein, the major side effects have been an initial febrile response, fatigue, malaise, marrow suppression, and inhibition of hair growth. So far, side effects have been rapidly reversible on lowering of dosage. Present studies with the use of lymphoblastoid interferon and bacterial-derived interferon employ materials of significantly greater specific activity. Such experience suggests that the same general side effects that were limiting with leucocyte interferon are present with interferon produced from recombinant DNA by bacterial as well as with lymphoblastoid interferon.

Introduction

In this paper I shall review our own progress on the use of one agent, human interferon, as a therapeutic for human viral disease. In this discussion interferon is to be thought of as a lymphokine. Fortunately, as a result of recombinant DNA technology, it is now the best characterized and now readily available member of this group of biologically active substances. Hence with the present availability of interferon from this source as well as from buffy coat leucocytes and mass cultures of transformed human B lymphocytes (lymphoblastoid cells), its pharmacological evaluation is the most advanced. It is also clear that much more clinical work needs to be done.

The public media have given much attention to interferon in recent years. Unfortunately, the potential of its broad spectrum of action on viruses and tumour cells has been stressed without consideration of our very limited knowledge of its scope of efficacy. In addition, there has been no discussion of its pharmacological limitations. For example, it has definite side effects even though these are reversible in most situations, and its high molecular mass limits distribution even after intravenous administration. The antiviral and antitumour agent areas are rapidly developing. In the present state of knowledge, it is difficult to assess accurately the possible role of any single agent.

Although there has been much interest in the clinical application of human interveron in viral infections, little material has been produced for this purpose over the years. Fortunately, since 1972 our group has been supplied with interferon by Dr Kari Cantell of the State Serum Institute in Helsinki, Finland.

Results and discussion

Interferons and varicella–zoster infections

The effect of human leucocyte interferon was tested in three placebo-randomized double-blind trials involving 90 patients with cancer (Merigan *et al.* 1978). Higher doses of more purified interferon in the second and third trials produced a significant ($p < 0.01$) decrease in cutaneous dissemination. No dissemination occurred in those receiving the highest dosage (5.1×10^6 u kg^{-1} d^{-1}) ($p < 0.035$).† The number of days of new vesicle formation in the primary dermatome decreased (mean 2.2 days; $p < 0.05$) in this group. Treated patients had a trend toward less acute pain and significantly ($p < 0.05$) diminished severity of post-herpetic neuralgia at the two highest dosage levels. Visceral complications were one-sixth as frequent in interferon recipients. Interferon at high dosages thus appeared effective in limiting cutaneous dissemination, visceral complications, and progression within the primary dermatome.

More recently, we have analysed the results of a fourth placebo-controlled randomized double-blind trial in the same population, involving only 48 h of therapy at the dosage used in the third trial (Merigan *et al.* 1981). However, in this trial there was no effect on acute pain or disease progression in the primary dermatome. A modest but significant effect was noted in that distal cutaneous spread was diminished in the treated patients compared with controls, and the treated patients had a diminished severity and duration of post-herpetic neuralgia. The results of this study indicated that in addition to a high dosage, a significant duration of treatment with human leucocyte interferon is required to modify herpes zoster infections in patients with cancer.

Because of our results on zoster, we have also undertaken to extend this approach to primary infection by the same virus, i.e. varicella in children with cancer. Eighteen patients who developed varicella while being treated for a malignancy received human leucocyte interferon in a small randomized placebo controlled trial (Arvin *et al.* 1978). These studies were conducted only with the lower two doses used in our initial zoster trial, i.e. 4.0×10^4 u kg^{-1} or 2.55×10^5 u kg^{-1}. The average treatment time in this trial was 6.4 days. Complications of varicella occurred in six of the nine placebo recipients but were observed in only two of the interferon recipients. In addition, the interferon was tolerated without significant side effects. Because of these results, we have just completed another randomized double-blind study of human leucocyte interferon for the treatment of early varicella in 44 immunocompromised children with cancer. Here, we have also observed a diminished spread of infection in the skin and visceral complications (Arvin *et al.* 1982*a*).

Interferons in chronic viral infections

We have also attempted to treat chronic viral infections, first focusing on neonates. Although leucocyte interferon at high dosage transiently diminished cytomegalovirus viruria (CMV) in infants, side effects were recognized (Arvin *et al.* 1976). Because of the decreased weight gain and transient liver enzyme elevation, and the transient nature of the antiviral effect, these observations were not pursued further with the interferon preparations then available. Now that interferon derived from recombinant DNA is available in a pure form, we are returning to the study of interferon's action on CMV infections.

We have recently concluded studies of three infants with rubella in whom we could measure virus excretion. Although pharyngeal shedding ceased in one of the three after treatment, there

† Units with reference to the W.H.O. reference standard.

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was no constant effect on virus excretion in the urine or the pharynx of the other individuals (Arvin *et al.* 1982*b*). Hence we conclude that in neonatal infections, although large doses of interferon can be used, the immune deficits associated with the infection significantly impair the usefulness of interferon therapy.

On the other hand, we have had more success in using interferon in the treatment of chronic hepatitis B infection (Scullard *et al.* 1981*b*). Over the past 5 years, 32 patients with chronic hepatitis associated with persistent hepatitis B virus infection have received 16 courses of human leucocyte interferon, 5 courses of adenine arabinoside and 21 courses of these two agents used in combination. The aims of this study were (*a*) to follow the effects of these agents on hepatitis B virus markers in serum and liver tissue; (*b*) to evaluate different regimens in order to select one with a reasonable toxicity/efficacy ratio that could be used in a large-scale controlled double-blind trial; and (*c*) to attempt to identify patients' clinical and virological characteristics that might influence the outcome of therapy (Scullard *et al.* 1981*b*).

Multiple cycles of adenine arabinoside and human leucocyte interferon were the most effective régime and permanently eradicated Dane particles (measured by serum DNA polymerase activity) in 44% of patients thus treated. Patients with chronic active hepatitis or who were females or who had a recent history of steroid therapy responded significantly better. Only 9% of untreated patients lost DNA polymerase activity over a similar period. Successfully treated patients had improved liver biopsies and reduced serum transaminase levels (Scullard *et al.* 1981*a*) compared with those who did not respond to therapy. Sera from patients who responded to therapy were no longer infectious for chimpanzees (Scullard *et al.* 1982). Significant neurotoxicity was seen in 44% of patients treated with adenine arabinoside especially when treated with concurrent human leucocyte interferon and adenine arabinoside (Sacks *et al.* 1981).

We have now begun treating patients with sequential courses of human leucocyte interferon and adenine arabinoside monophosphate (the soluble monophosphate derivative of adenine arabinoside monophosphate) (Smith *et al.* 1982). Ten young adult male patients with chronic hepatitis B virus infection and positive HBeAg and DNA polymerase were treated with alternating courses of 7–28 days of adenine arabinoside monophosphate at 5–7 mg kg^{-1} and 28 days of human leucocyte interferon; 3 different regimens were given on an out-patient basis. All patients responded with a decrease in their DNA polymerase and in one patient the DNA polymerase remained undetectable 6 months after treatment was stopped. The major side effect, which only occurred in those patients receiving adenine arabinoside monophosphate at 7.5 mg kg^{-1}, was severe muscular pains. This study demonstrated the feasibility of administering adenine arabinoside monophosphate and human leucocyte interferon to out-patients. Based on data from this and other studies it is now possible to use a non-toxic regimen which includes 28 days of adenine arabinoside monophosphate at 5 mg kg^{-1} in a larger controlled study to answer the question of long-term efficacy. Such a study is now under way.

Recently we have been testing in chronic hepatitis B infected patients a pure preparation of IFN-α2 produced in bacteria by means of recombinant DNA. Our initial findings indicate that it has similar side effects and efficacy in Dane particle suppression to leucocyte interferon. An important question yet to be answered is whether a greater dosage of the pure bacterial-derived species could be tolerated and, if so, what would be the acute and long-term effects of such dosages.

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Discussion

In discussion it appeared that there may be neuronal receptors for IFN. Growth inhibition of neuroblastoma cells has been found. Dr Merigan also agreed that acute enhancement of liver enzymes always seemed to occur in patients who ultimately showed suppression of hepatitis B virus replication.

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