

Review Article

Interferon — the clinical experience

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Summary

Recent trials with interferon, in particular those using pure, recombinant interferon, have provided us with improved data (compared with those obtained in early studies) and show that interferon does hold some promise as a therapeutic agent.

When used in the treatment of viral disease, interferon has shown itself to be quite effective in reducing viral titres. While not as effective against cancer, interferon has limited tumour growth, reduced the appearance of metastases and led to a general improvement in patient condition in many cases.

This article discusses some of the recent results obtained with interferon in the treatment of viral disease and cancer.

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Interferons are proteins which provide one of the many natural defences against viral disease, and which, largely as a result of a scarcity of this material, have been surrounded by mystique. This mystique is being rapidly eroded owing to the availability of ever-increasing quantities of interferon produced by new techniques, particularly by recombinant DNA technology. This progress has led to an explosion of articles on interferon in the media, and certainly in the popular press.

The interferons currently in use have been directly or indirectly produced from three cell types: leucocytes (alpha interferon), fibroblasts (beta interferon) and T lymphocytes (gamma or immune interferon). There is evidence for the existence of 2 subtypes of beta, 1 of gamma and at least 12 of alpha interferon. Current yields of interferon are approximately 10^6 U/l from blood or 10^{10} U/l from recombinant DNA bacterial cultures. Since the daily requirement for a single cancer patient may be in excess of 10^6 U (the maximum obtainable from one blood donor), the problem of supply and demand is clear. Whether the interferon is produced from blood or by bacterial or yeast cultures, the demand and rewards are so high that there are presently in excess of 30 companies engaged in interferon production in the USA alone.

This article briefly summarizes some of the clinical results obtained recently in both prophylactic and therapeutic trials with 99% pure interferon.

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Anti-viral effects of interferons

Cytomegalovirus

This virus can have severe effects on the fetus or in immunosuppressed patients, and can lead to infant mental retardation or death. Treatment of infected infants with interferon has produced some encouraging results. In one trial viruria was completely inhibited in all 9 patients studied,¹ whereas in another study 3 out of 5 patients reacted positively but weakly.² Reports agree that higher doses of interferon diminish viruria, although in positively responding patients the effect is transient and virus secretion returns to original levels when treatment stops.

A study of immunosuppressed patients indicated that non-treatment led to the earlier and more frequent occurrence of viruria than is the case when interferon treatment is administered.

Hepatitis

Chronic active hepatitis B is a promising disease as regards use of interferon therapy. Circulating Dane particle markers decrease with interferon therapy, and after prolonged treatment all B virus markers disappear in some patients.³ In order to achieve this, leucocyte interferon 900×10^6 U in a treatment schedule of 4 - 6 months with a follow-up period of 6 - 12 months was required. Addition of adenine arabinoside helped to achieve a long-lasting effect, 50% of the patients showing no Dane particles for several months after withdrawal of treatment.

Herpes

Beneficial effects in patients with labial and genital herpetic lesions have been noted with the application of interferon ointment. In one study interferon-treated patients suffered only half the number of lesions of those occurring in a control group receiving placebo.⁴ Disseminated herpes zoster also responded favourably, doses of interferon of $1 - 80 \times 10^6$ U/d being administered intramuscularly. A decrease in pain, less involvement of visceral organs and shorter healing times were noted.⁵ Interferon eyedrops have been used to good effect in human herpetic keratitis.^{6,7} A decreased rate of recrudescence was observed, this being greatly enhanced by debridement.

Influenza

Large-scale studies in the USSR⁸ indicated that prophylaxis against influenza could be obtained by the inhalation of low-dose interferon in aerosol form. These results have not been confirmed in the West, where it is claimed that the interferon available to the Soviet public at a cost of \$1 per dose is of such low strength as to be ineffective. A separate study showed that in patients suffering from influenza fever could be reduced by treatment with interferon (D. Ikic — unpublished data).⁹

Marburg virus

One (accidental) case has been reported where a patient was treated with 3×10^6 U twice a day for 2 weeks. There was a rapid

decline in viraemia and the patient recovered.⁹ This disease has a high mortality rate, but since the abovementioned report involved only 1 patient and no controls no definite conclusions may be drawn.

Rhinovirus (common cold)

Interferon nasal sprays have received much attention in common cold (or rhinovirus) prophylaxis and therapy.^{10,11} Eight volunteers received a nasal spray of interferon before exposure to rhinovirus, and only 3 of them subsequently developed mild symptoms; of a control group of 11 volunteers all but 1 developed mild to severe colds. Other studies have estimated a 'general reduction in illness' of 40% (in terms of lower viral titres) in interferon-treated patients.

In the treatment of various virus infections it has been found that the effectiveness of interferon increases in direct proportion to the concentration of it applied to the affected area. Parenteral administration of interferon requires much higher dosage in order to achieve the same local high interferon titre obtained with local application. This is clearly demonstrated in the treatment of warts, disappearance of lesions having been reported after local applications of interferon (M. Ho — unpublished data).

Anti-cancer effects of interferon

So far, interferon therapy has been attempted in only a few hundred cancer patients. There has been remission in some cases, certain cancers responding better than others. It is not yet possible to compare interferon therapy with other methods because there have been no randomized trials. Laboratory studies have shown that the effect of interferon on cell proliferation appears to be very general where all cells of an organism are sensitive to some degree. In some cases interferons inhibit the growth of tumour cells more than that of normal cells, but in other situations normal cells have been as sensitive. *In vivo* inhibition of the growth of cells found to be insensitive *in vitro* indicates that the effects of interferon are probably indirect, and may be mediated by the ability of interferons to enhance the functions of cells of the immune system and to cause expression of surface antigens on tumour cells.¹²

Malignant lesions of the haematopoietic and lymphoid systems

Leukaemic patients respond to interferon treatment but the disease is not cured. The average survival time increased,¹³ the majority of patients responding positively (all 5 patients with acute lymphocytic leukaemia, 1 of 3 with acute granulocytic leukaemia, and 5 of 7 with B-cell chronic lymphocytic leukaemia).^{14,15}

In patients with Hodgkin's disease a disappearance of bone infiltration and total or partial remission of symptoms has been shown (G. Emödi — unpublished data). Non-Hodgkin's lymphomas have also responded favourably to interferon therapy. Three out of 3 patients with nodular lymphocytic lymphoma experienced a reduction in tumour size.¹⁶ Similar results, with 3 out of 6 patients responding positively, were obtained independently,¹⁷ and in another study 6 out of 8 patients showed disease regression, including patients refractory to chemotherapy and with extensive disease.¹⁸ Two such patients lacked all evidence of disease after 8 - 12 weeks of interferon therapy, and remained in that state for more than a year.

Treatment of multiple myeloma has also been attempted. The disease has been reported to regress and then advance in spite of interferon treatment, but separate studies have reported that 4

out of 4, 5 out of 9 and 3 out of 11 patients with multiple myeloma responded positively.¹⁷⁻¹⁹

With the advent of interferon manufactured by recombinant DNA methods, therapy with a pure homogeneous protein preparation is possible. Early results with leucocyte interferon (IFLrA from Hoffmann-La Roche) show that in 7 out of 16 patients with advanced metastatic cancer the tumour regressed; in a separate study 2 patients with lymphomas both responded well.^{20,21}

Sarcomas and carcinomas

One of the most promising applications for interferon treatment is juvenile laryngeal papilloma, possibly because of its viral nature. All reported cases seem to regress with interferon treatment, but tumours reappeared after treatment was stopped.²²

Breast cancer treatment also gave promising results. In one trial 5 out of 23 treated patients showed partial remission and 4 an improvement in their condition; 8 remained stable and in 6 the tumour progressed.²³ Other studies have reported a positive response in 7 out of 8 and 3 out of 5 patients.¹⁸

Treatment of seropapillary ovarian cancer in 5 patients showed a positive response in 4, with a decrease in tumour volume but no complete remission.²⁴

Development of metastases in patients with osteosarcoma may be inhibited by treatment with interferon. In studies involving relatively larger numbers of patients it was found that 73% of interferon-treated patients survived, compared with 35% of controls (H. Strander — unpublished data). In one study metastases were found in 10 out of 22 controls compared with none of the 10 interferon-treated patients, while in another 2 out of 6 treated patients developed metastases.

Miscellaneous diseases

Treatment of multiple sclerosis has been attempted, but results are difficult to evaluate because of the lack of reliable parameters for assessing the clinical condition of these patients. In spite of this, some encouraging results have been reported.²⁵ Attempts to improve the condition of patients with active rheumatoid arthritis have also been made, although no definite conclusions were drawn.²⁶

Administration and contraindications

Interferon may be administered parenterally or locally. Local administration can be either by topical application in ointment form (as in the treatment of herpes) or by intralesional injection (as with some wart treatments). Parenteral administration is the method of choice for a systemic viral disease or in cancer therapy, but suffers from the disadvantage that the amount required to reach a high concentration at any specific site is very much larger than that required in topical applications, simply because effectiveness increases in direct proportion to the concentration of interferon.¹⁸

Side-effects of interferon therapy include fever, chills, myalgia, headaches, fatigue and gastro-intestinal disturbances. Fatigue is perhaps the most serious of these. In addition, reversible leucopenia and granulocytopenia as well as transient numbness of the hands and feet may occur. Some side-effects, such as headaches, disappear after some days of continued treatment. These side-effects appear to be inherent in the interferon molecule and are not associated with impurities, since treatment with recombinant interferon does not appear to result in less severe side-effects.

Problems associated with interferon therapy

The earlier trials begun in the 1960s suffered the problems of erratic supply and impurity of interferon preparations. These samples contained less than 1% interferon, in contrast to the greater than 99% purity of current recombinant DNA samples. Most trials have been undertaken with natural interferon, which is a mixture of interferon proteins (even when highly purified). The effects of the different interferons in various clinical conditions have not been assessed, and it is only with the advent of recombinant DNA technology that this area can be investigated.

The identification of patients who might benefit from interferon therapy and the preparation of effective treatment schedules is extremely difficult, partly because of the lack of information regarding dosage and administration. It was recently found that there are at least two different interferon receptors.²⁷ This may make it necessary to evaluate the responsiveness of each condition or patient to different interferons by receptor analysis prior to treatment. The failure of some patients to react positively to treatment whereas others with the same condition show signs of improvement may be at least partially a result of this situation.

The future

With the availability of interferon for large-scale trials, more information regarding its use should be forthcoming within the next few years. This increased availability is largely the result of improved production techniques and the bacterial and yeast production of single interferons. Since there are many different interferons and possibly different receptors it may be that individual assessment is necessary before the institution of therapy. So far, clinical work has involved fibroblast and leucocyte interferon, and it is only now that the third type, produced from T lymphocytes (immune interferon), may begin to show its potential. Laboratory work shows that this interferon is quite different from the others and is more effective in inhibiting cell proliferation.

Recent research²⁸ has shown that by using recombinant DNA technology it is possible to create hybrid interferons with different biological activities from the parent molecules. It may be that in such hybrids lies the greatest potential for the clinical application of 'tailor-made' interferons.

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