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Prospects for the Medical Use of Interferon in 1984

Bosko Postic, MD* and Julio C. Arroyo, MD*

Interferon, a natural and wide spectrum antiviral polypeptide that was discovered in 1957, has been extensively described. In addition to its antiviral effect, interferon has been found to suppress tumor growth and modulate the immune response. Until 1980, interferon was primarily prepared for clinical trials in human leukocytes derived from the buffy coat of whole blood. A major breakthrough occurred in the late 1970s when human interferon was produced by DNA recombinant methods in such heterologous cells as bacteria (genetic engineering). Interferon is not commercially available in 1984, but it may, based on clinical trials in humans, become part of combination therapy for certain cancers. It also holds promise for the treatment of chronic active hepatitis due to hepatitis B virus. Interferon has been effective in herpes virus-induced infections, suppressing reactivation episodes as well as the signs and symptoms of varicella-zoster virus infections. Prophylactically, but not therapeutically, interferon exerts a favorable effect on cytomegalovirus (CMV) infection; however, interferon trials are needed in catastrophic virus infections where no established (or effective) therapy exists. Prophylactic intranasal application of interferon was shown to suppress the symptoms of the common cold. The role of interferon treatment in the acquired immunodeficiency syndrome (AIDS) and its associated opportunistic infections and/or Kaposi’s sarcoma requires further study but shows promise, particularly for the latter.

As noted, live or inactivated viruses may serve as inducers of interferon production in cultured cells and intact animals. Within a few hours after a suspension of virus is intravenously injected into an animal, high-titered interferon appears in the plasma (7,8). The production of interferon may also be stimulated by synthetic polynucleotides such as the polyinosinic-polycytidylic acid (9), by antigens (10), and by endotoxin (11).

Interferons are now classified into three types (Table 1). Alpha interferon is produced by human leukocytes

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**Table 1**

<table>
<thead>
<tr>
<th>Type</th>
<th>Common Inducer</th>
<th>Produced By</th>
</tr>
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<tbody>
<tr>
<td>Alpha</td>
<td>Virus, live or inactivated</td>
<td>Leukocytes (Mononuclear mostly)</td>
</tr>
<tr>
<td>Beta</td>
<td>Synthetic, double stranded polyribonucleotide</td>
<td>Fibroblasts in culture</td>
</tr>
<tr>
<td>Gamma</td>
<td>Antigen</td>
<td>T (Helper) Lymphocytes</td>
</tr>
</tbody>
</table>

Submitted for publication: May 25, 1984
Accepted for publication: July 6, 1984
which usually have been stimulated with a myxovirus. Until recently it has served as a material for clinical trials (4,12). Beta interferon can be stimulated in tissue culture with viruses or synthetic polyribonucleotides. Interferon can also be liberated by T-cells upon contact with antigen. This lymphokine, previously termed "immune" interferon (5,10), is now called gamma. All three interferons are antiviral in their effect, though they differ as to their cell source and the method of induction. Antigenic determinants are specific to the type and identifiable by monoclonal antibody.

The biologic effects of interferon also constitute a triad. There is (a) an antiviral effect, (b) an inhibitory effect on cellular proliferation, and (c) an immuno-modulator. These effects characterize interferon as a cellular protein product with a high specific activity, about 4 x 10^8 mg protein per unit, which is comparable to a hormone (5). The specific activity relates to the antiviral effect, and this potency could be quantitated and standardized as international units through a human interferon standard preparation from the National Institutes of Health.

The antiviral effect of interferon is not direct. Interferon is absorbed on cells and produces an antiviral state in them by inducing the synthesis of new proteins. Such a protein is the enzyme responsible for the synthesis of a new 2',5' isoadenylate, which activates an intracellular ribonuclease that is capable of degrading the messenger RNA involved in the biosynthesis of the infecting virus (13). A protein kinase is also induced which leads to phosphorylation and, thereby, depression of an initiation factor needed for viral protein synthesis (14). Unlike antibiotics that directly attack bacteria, interferon requires the host cell's participation for its antiviral effect. It follows that this effect is inhibitory and not virucidal. Therefore, the antiviral effect of interferon in animal and human cell culture is suppressive and not eradicative. The patient's preserved immunity is needed to complete the antiviral effect, that is, lead to cure from infection.

The mechanism of the cell inhibitory effect of interferon remains unknown. In certain virus-induced tumors, the antiviral effect of interferon may also have an indirect antitumor effect. However, interferon is also effective in tumors that are not viral in origin (15). The cell inhibitory effect of interferon has also expressed itself as a side effect in patients treated for leukopenia. Fortunately, the effects were reversible when interferon therapy was discontinued.

Interferon may be both stimulatory and inhibitory to immune function, depending on antigen stimulation timing (16) and interferon dosage. Interferon may suppress antibody formation (17), but it enhances the natural killer lymphocyte function (5).

Interferon is also a weak antigen. Antibodies to interferon may sometimes be neutralizing (18), suppressing the antiviral and other biologic effects of interferon.

In most instances, interferon displays an interesting characteristic of species specificity by being active (antiviral) only in cells of the homologous species. However, many interspecies "crosses" have been identified.

Cloned Interferon

As mentioned, most interferon for clinical trials has been produced in human leukocytes by the "Cantell method" (4,12), as an intentional and ingenious by-product of blood banking. Leukocytes are separated from whole blood and used for the production of interferon after interaction with the inducer (an inactivated myxovirus). The method, however, is quite complex and produces a relatively low yield because of the extensive purification required (one unit of blood (500 ml) can produce one million units of interferon, or the equivalent of 4 micrograms (5)). Even after this purification, the product is semipure.

Goeddel and co-workers produced human leukocytic interferon in bacteria using DNA recombinant techniques (19). They recovered the gene responsible for the production of interferon in the human leukocyte and then cloned it in Escherichia coli after introduction by a plasmid. This method allowed major production of interferon and the initiation of more extensive clinical trials. In addition, interferon could be purified from other bacterial constituents by the use of monoclonal antibody (6). Several groups of molecular geneticists achieved similar results concurrently (5).

Interferon Therapy in Catastrophic Viral Disease

There is little information regarding the possibility of interferon intervention to combat human viral diseases. Hence, projections for the therapeutic role of interferon are derived mostly from animal studies.

Experiments with rabbits demonstrated their resistance to challenge with street rabies virus when they were stimulated to produce interferon by a synthetic polyribonucleotide. Better effects were seen when the injection of the interferon inducer preceded the inoculation of virus than when the treatment was started after exposure (20,21). Administration (intravenous or intramuscular) of rabbit interferon was also prophylactically protective (22). In the same experimental model, therapy with interferon, via intracranial installation by an intraventricular cannula, resulted only in prolonging the incubation period (23). As to the use of interferon in the prophylaxis of rabies in humans, there is already an effective immunologic postexposure treatment (24).
The prospects for using interferon to treat rabies victims seem slim, since victims are recognized late in their course when most of the viral-inflicted damage becomes irreversible.

It is conceivable that interferon may be a therapeutic option in other catastrophic viral diseases such as those produced by Ebola and Lassa fever viruses. Due to the location of these cases, a trial of interferon will probably be limited to individual patients. A laboratory worker, treated with antiserum to the virus and large doses of interferon given experimentally to monkeys who had been inoculated with Ebola virus failed to protect them from death (26).

Systemic and intrathecal interferon therapy may be worthwhile in cases of putative viral encephalitis. Prophylaxis with interferon may be the only antiviral measure feasible after an unimmunized person has been exposed to an encephalitogenic virus. Mice could be protected from Japanese B viral encephalitis by prophylaxis with an interferon inducer (27). Moreover, combined immunization and interferon induction caused enhanced protection in mice challenged with that virus (28).

**Interferon in Chronic Hepatitis B Infection**

Merigan and his group at Stanford University have extensive experience with human leukocytic interferon and recombinant alpha interferon in chronic hepatitis B infection (29-31). Their patients were chronically antigenemic with HbsAg and HBeAg, which indicates persistent viremia. Interferon and adenine arabinoside, separately and in combination, produced antiviral effects, the most consistent of which was the suppression of Dane particles in plasma, i.e., reduction of viremia. Leukocyte interferon and adenine arabinoside in combination produced a virologic and a clinical cure in three out of 32 patients. Approximately half of the patients experienced only transient improvements (30). The use of recombinant interferon alpha also allowed the titration of the daily intramuscular dose; there was a greater suppression of the hepatitis B virus DNA polymerase, i.e., a reduction in the magnitude of viremia, with higher doses (50 and 68 million units) than with lower ones (3 and 9 million units a day, intramuscularly) (31).

**Interferon Treatment with Herpes Infection**

This topic was extensively reviewed by Hirsch and Schooley (32). Human leukocyte interferon was effective in the treatment of herpes zoster in patients with cancer (33). A controlled trial of prophylactic human leukocyte interferon resulted in delayed shedding of the cytomegalovirus (CMV) and a lower incidence of viremia after renal transplantation (34). Interferon reduced the signs of CMV infection in renal transplant recipients. Interestingly, opportunistic superinfections by Aspergillus fumigatus and Pneumocystis carinii occurred in patients who were given placebos but not in those treated with interferon (35). Susceptibility testing of six CMV isolates with beta interferon revealed that this virus was inhibited by interferon in cell culture, but to a lesser degree than the very sensitive vesicular stomatitis virus (36). Antiviral treatment of disseminated CMV illness in renal transplant recipients has not been successful thus far (37), and currently there is no recommended treatment for established CMV infection in humans. Investigational purine and pyrimidine analogues hold some promise, based on in vitro testing (32).

Short-course human leukocyte interferon was effective in the treatment of herpes zoster in patients with cancer. Antiviral effects could be observed in a placebo-controlled, randomized, double-blind trial involving only 48 hours of therapy (38).

A reactive herpes simplex infection could be prevented by human leukocyte interferon administered before an operation was performed on the trigeminal root (39,40). In this well-conducted trial by the investigators from Pittsburgh, an intramuscular dose of interferon was administered, 7 x 10^6 units per kg per day for five days, beginning the evening before the operation. The magnitude of virus shedding was greatly reduced postoperatively in interferon vs placebo-receiving patients. One could also anticipate beneficial effects of interferon in genital herpes, although effective therapy is already available in this instance with acyclovir (32). Interferon is also effective in decreasing the acute symptoms and possibly any recurrences of herpes simplex keratitis (41). In this disease, optimal results were produced by combining trifluorothymidine with interferon (4).

**Interferon in Respiratory Diseases**

In experimentally-induced instances of the common cold in humans, intranasal application of leukocyte interferon resulted in the reduction of symptoms and virus shedding (42). Intranasal alpha interferon, produced by the recombinant DNA technique, also prevented the experimental rhinovirus infection and illness in humans (43). However, intranasally administered interferon was not without side effects. Some volunteers treated for five days or longer reported bleeding mixed with mucous nasal discharge and superficial erosions of the nasal mucosa (44). The most efficacious use of interferon against the common cold is likely to be by short, prophylactic administration.
Interferon has not been effective thus far in controlling clinical influenza in humans. However, the virus is sensitive to it. With the increased availability of interferon and better ways of administration into the respiratory tree, clinical trials for the treatment of lower respiratory infections are urged (45).

Antitumor Trials in Humans with Interferon

This field was opened with the experimental work of Gresser (15). Strander, Cantell, and associates were successful in treating osteogenic sarcoma with prolonged intramuscular administration of leukocyte interferon (46). A well-documented antitumor trial was conducted by Gutterman and coworkers, and partial remission was effected in 6 of 10 patients who had breast cancer and in 3 of the 6 multiple myeloma cases. Four of the 11 patients with malignant lymphoma also showed some beneficial effect. The response to interferon depended on the previous response to chemotherapy; none of the patients who had been unresponsive to chemotherapy experienced a complete remission when they were treated with interferon. Only 1 of 9 patients in this category had a partial remission (47). A tumor-reducing effect was noted when three patients who had nodular lymphoma were treated with human leukocyte interferon (48). Even more encouraging results were recently obtained when recombinant leukocyte interferon was administered to homosexual men who had Kaposi's sarcoma, producing a beneficial effect in 5 of the 13 (49). Similar results were reported from the National Institutes of Health (50). Alpha interferon induced in human leukocytes produced a remission in hairy-cell leukemia in all seven of the patients who were being treated by Quesada and associates (51). No other form of treatment has been found so consistently effective in this disease. Recombinant interferon showed some beneficial effect in 4 of the 8 patients who had advanced cancer (52).

Interferon, applied intramuscularly and, particularly intrathecally, was found to be effective in two patients with extensive tumor loads due to the human wart virus (53).

Gamma interferon produced a greater antitumor effect in mice bearing sarcoma MC-36 than did a beta preparation (54). Trials with this interferon for the treatment of cancer in men are not yet available for review.

In summary, interferon may become an adjunct in antitumor therapy. While most of the effects observed in clinical trials were temporary and not eradicative, interferon may yet become part of combination therapy for certain cancers.

Undesired Side Effects of Interferon

The clinical use of interferon is presently limited, to a certain degree, by its many side effects (Table II). All appear to be reversible and most are dose dependent.

The severity and frequency of side effects could have been affected by impurities in the earlier leukocyte preparations (55); however, purified, cloned interferon also produces undesired effects which are indistinguishable from those seen with leukocytic interferon.

Virtually every patient receiving interferon experiences fever and chills, the severity of which is dependent on both dose and frequency of administration (56-58). All three classes of interferon are pyrogenic. Both alpha and beta interferon were found to enhance the potential of human monocytes to produce the endogenous pyrogen, interleukin-1 (59). However, exposure of interferon-pretreated monocytes to endotoxin was required for the actual secretion of interleukin-1; interferon alone was unable to induce its secretion. Whether the influenza-like, febrile illness caused by interferon is due to interleukin-1 is still undetermined. Some suggest that interferon is intrinsically pyrogenic (a second endogenous pyrogen) (57,60). Interestingly, the production of virus-induced interferon was enhanced by fever in rabbits (61).

An even more limiting effect, also dose-dependent, is the excessive fatigue that many patients experience when treated with interferon. Unlike fever, this malaise tends to be cumulative and progressive (56).

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic</td>
<td>Fever, chills, anorexia, fatigue, myalgia</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Leukopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Renal</td>
<td>Proteinuria</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Increased transaminases and alkaline phosphatase, depression of cytochrome P-450</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Headache, numbness, paresthesias, confusion, disorientation, seizures, abnormal EEG, drowsiness, irritability</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Relative adrenal insufficiency</td>
</tr>
<tr>
<td>Cardiac*</td>
<td>Arrhythmias, myocardial infarction</td>
</tr>
<tr>
<td>Immunologic</td>
<td>Suppressed NK activity and antibody production</td>
</tr>
</tbody>
</table>

*Likely secondary to systemic effects
Proteinuria has been occasionally described and can last up to two weeks after treatment is discontinued (56). Interferon, injected alone or induced by lymphocytic choriomeningitis virus, was found to induce glomerular lesions in newborn mice (62,63). In a patient receiving recombinant interferon, interstitial nephritis presented as nephrotic syndrome. The renal dysfunction was dose dependent and reversible (64).

Hepatic structural damage was shown in interferon-treated mice. In humans, transient elevations of transaminases and alkaline phosphatase are frequent complications of interferon administration (56). Neurologic dysfunction is not commonly detected, consisting mainly of drowsiness, irritability, and confusion. However, all of the patients tested had abnormal electroencephalograms, even if they were otherwise normal neurologically (65). Even the heart appears to be affected by interferon, associated with arrhythmias and myocardial infarction. However, most of the patients observed were older and had evidence of preexisting heart disease. It is possible, therefore, that the systemic effects of interferon are a major cardiac stress (66). Relative adrenal insufficiency may also represent an undesired effect of interferon (67).

The stimulatory and depressive effects of interferon on the immunologic system can be both beneficial and harmful to the host. In a trial with recombinant leukocyte interferon, five cancer patients developed peripheral herpes simplex lesions after therapy was initiated. Although enhancement of natural killer cell activity by interferon has been frequently observed, interferon can also depress natural killer cytotoxicity in vivo (68).

Lastly, interferon can affect the metabolism of other drugs through depression of the cytochrome P-450 system, thus prolonging the half-life of drugs like diphenylhydantoin and possibly adenine arabinoside (69).

Summary

The role of interferon in the therapy of patients has not yet been defined and is a subject for continuing clinical studies. The availability of cloned interferon has probably shortened the interval required for investigational studies before therapeutic use. It is difficult to project a date when interferon will be routinely used in the United States. The demonstrated, albeit transient, effect of interferon in antitumor therapy may allow its introduction as an approved medication. One could project a place for interferon in the treatment of chronic hepatitis B infection. Trials of interferon treatment of delta virus super-infections are also needed. Interferon is a broad spectrum antiviral agent inhibiting most pathogenic viruses in experimental systems. Therefore, it may be useful in treating retrovirus-induced disease in humans. Catastrophic viral diseases, such as a viral encephalitis, may be considered for a trial of interferon. Respiratory virus disease is mostly self-limiting; since the side effects of interferon treatment seem to outweigh its therapeutic benefits, its use as a major therapeutic aid seems unlikely. However, the local side effects may be avoided if short interferon courses are used prophylactically for the common cold. Last, but not least, interferon treatment holds definite promise in herpes virus infections characterized by latency and recrudescence. This may have particular value for patients who are immunosuppressed. The time has arrived for the practicing physician to become acquainted with interferon, with its varied biologic effects, and its potential in the therapy of viral and neoplastic diseases affecting humans.

Acknowledgment

The authors thank Dr. Arnold Brown of Columbia, SC for his constructive review of this manuscript.

References

Interferon in 1984


