3

INTERFERON THERAPY IN ACUTE VIRAL ILLNESSES

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INTRODUCTION

Thirty years have elapsed since the discovery of interferon (IFN) as a naturally occurring biological substance with antiviral activity against a broad spectrum of RNA and DNA viruses, but reports of its use in clinical trials of acute viral infections have been surprisingly meager. There are several reasons for this, the major one being that for the first 20 years after its discovery, stocks were in very short supply, and when available, very expensive.

Additionally, when the subsequently discovered properties of the IFNs to suppress cell growth and modulate the immune response

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became known, clinicians were excited with the possibility of finding a new approach to the control and cure of cancer. At this point, the antiviral activity of IFN seemed to have become of secondary importance to physicians, for after all, unlike cancer, many of the cases of viral disease for which IFN was being used were not life-threatening. The recent appearance of several antiviral chemotherapeutic agents like acyclovir, active against many of the viruses which are responsive to IFN, may have also led to the paucity of clinical trials of IFN as an antiviral agent. With the advent of newer technology, increasing amounts of the different types of IFN were produced and during the last few years genetically engineered recombinant IFNs have become available cheaply and in vast amounts, allowing for their use in clinical trials of viral diseases as well as cancer.

Tissue culture and animal studies have shown that IFN has a remarkable antiviral effect on most viruses but the effect is not a direct one. IFN inhibits virus replication and spread in the cellular microenvironment by activating several intracellular antiviral enzymes whose functions are to prevent recognition of the virus, translation of viral mRNA and assembly of new viruses. Normally the presence of a virus leads to the protective production of IFN molecules by the cell and these are then secreted into the extracellular spaces and into the blood stream where they will interact with IFN receptors and other cells leading to the induction of an antiviral state. Under certain conditions, and for reasons not as yet apparent, this IFN system may not be activated and the virus will replicate and spread uncontrolled until overwhelming infection leads to the demise of the patient. This has been reported to occur in cases of fulminant hepatitis, herpes encephalitis and in the terminal stage of AIDS, and has been termed the "IFN deficiency syndrome" (1). The giving of exogenous IFN in these cases has led to activation of the IFN system and has proved to be life-saving.

The main stimulus for pursuing clinical trials of IFN in viral disease came from Merigan and his co-workers in Stanford, California. It is more than 10 years since they began their trials to prove the efficacy of IFN in the prevention and treatment of herpes infec-

tions, particularly in the immune-suppressed host. They persisted in their efforts to establish IFN as a promising therapeutic agent in chronic viral hepatitis, and encouraged other workers in the field. Although some dramatic effects were often seen in individual cases, clinical trials as a whole were not decisive but encouraging. A major problem was the absence in the early years of well controlled trials. It appeared that IFN would be effective in certain cases whereas in others, the response was poor, if at all. This was most evident in the conflicting reports of the beneficial, or otherwise, effect of IFN in reducing or eliminating the viral markers in chronic viral hepatitis. All this has led to a feeling that IFN has as yet to prove itself as a good and efficient antiviral agent.

The following is a brief description of our experience in the treatment of 80 cases of severe, acute, life-threatening viral infections with HuIFN- , and a short review of published reports of the use of IFN therapy in a variety of acute viral illnesses.

PATIENTS AND METHODS

Since 1980, 80 patients of all ages suffering from life-threatening viral diseases have been admitted to an open study evaluating the effectiveness of HuIFN- treatment. Most patients were extremely ill with over 50% being in deep coma when entered into the study, usually as a last resort when all other therapies had failed. The trial was conducted according to a predetermined protocol which included pharmakinetic studies of several parameters of the IFN system before, during and after IFN therapy.

HuIFN- prepared by Drs H. Rosenberg and T. Bino at the Israel Institute for Biological Research, Nes Ziona, was given intramuscularly once a day in a 1ml solution of $3x10^6$ international units ($5x10^6$ units/mgm of protein). In small infants the daily dose was 70,000 to 100,000 units/kgm body weight. The course of treatment varied according to the illness or the patient's condition and response to therapy. For example, in cases of herpes infection of the skin, 1 to 5 (average-3) injections proved sufficient to stop the progress of the infection and for healing to begin, whereas in

fulminant hepatitis, the average course lasted about 10 days. In a case of laryngeal papillomatosis the treatment was continued for 10 months. Only patients receiving at least 3 daily injections of IFN- were included in the final evaluation.

The methods used in laboratory studies of the IFN system have been described in detail (2) and included the following:
1) Plasma IFN levels as an indication of in vivo IFN production in response to the viral infection.
2) Production of IFN- and IFN- by stimulated peripheral blood mononuclear cells (PMBC) in vitro, as an indication of the competency of cells to produce IFNs.
3) Evaluation of the antiviral state (AVS) of PBMC by testing whether they supported viral replication in culture or not.

RESULTS

One hundred and twenty patients ranging in age from 1 month to 70 years were treated with HuIFN- . Of these 80 were felt to fulfil the requirements of the protocol and are reported here (Table 1). The remaining patients were excluded because they were either proved later not to have an acute viral illness, or died before completing 3 days of therapy.

Acute progressive and fulminant hepatitis

There were 30 patients with acute hepatitis who developed acute hepatic failure and whose condition was serious enough to cause concern for their lives. Eighteen were confirmed as being caused by hepatitis A virus (11 of whom were in grade III+IV coma when treatment was begun and the rest grades I+II), 6 were due to hepatitis B virus infections (5 in grade IV coma), and 6 non A-non B hepatitis including two with herpesvirus infection, all of whom were in grade IV coma. Seventeen patients (57%) recovered of whom 10 were in grades III+IV coma. Our results indicated the best prognosis in adults and older children where 15/22 (77%) recovered whereas only 2/8 children below 4 years of age survived. In more than half these cases the IFN response was defective prior to IFN therapy and in almost every case the IFN system became activated

within a few days of beginning IFN therapy (3).

Table 1. Outcome of patients with severe viral illnesses treated with HuIFN- .

Diagnosis	Treated	Recovered	Unchanged	Died
Progressive or fulminant hepatitis	30	17	(2)	13
Encaphalitis	14	9	(2)	5
Herpes with immune-deficiency	19	19	-	-
Cytomegalovirus	6	3	1	2
Measles	4	3	-	-
Subacute sclerosing panencephalitis	3	-	3	-
Poliomyelitis (bulbar)	2	2	-	-
Varicella myelitis	1	1	-	-
Laryngeal papillomatosis	1	1	-	-
Total	80	55	4 (4)	21

( ) No. in brackets - cases recovered, but no evidence that IFN had any effect.

Acute viral encephalitis

There were 14 patients who were diagnosed as having viral encephalitis of whom 12 were in states III or IV coma. Eight cases were confirmed by serology as having herpes encephalitis, two measles, one varicella and in three the virus was not identified. Nine patients recovered, including 8/12 comatose patients. Nine patients were aged 1 month to 9 years, seven of whom survived. In 2 survivors there was no apparent change in the patient's condition while receiving IFN (4).

Herpes in immune-compromised patients

Seventeen cases with herpes zoster and 2 with herpes simplex received an average of 3-5 daily injections of IFN- . One critically ill patient with extensive spreading pyoderma gangrenosum and leukemia was treated for 16 days before recovering (5). In most

cases pain was alleviated within 1-2 days, no new lesions appeared after 2-3 days therapy and healing was noted within 3-5 days. In 3 cases it appeared that IFN- therapy had no effect on the infections after 3-5 injections. In general, the treatment was well tolerated, symptoms were alleviated and the usual course of the disease appeared to be shortened.

Cytomegalovirus infections

Six patients with CMV infections were treated. Of these three recovered: a 6-month-old with hepatomegally and severe immune-deficiency, another with severe hemolytic anemia and a 4-year-old with X-linked lymphoproliferative disease and pneumonia. Two others with lymphomas died of pneumonia, and the condition of a baby with chronic cytomegalovirus encephalitis remained unchanged.

Measles

Only very severe cases of measles with complication were accepted for IFN therapy. Of four cases treated, three had pneumonia and one encephalitis. Three children recovered, but a 1-year-old baby with IFN deficiency syndrome died with secondary infected pneumonitis.

Poliomyelitis

An adult and an infant, both with progressive ascending poliomyelitis affecting the bulbar area of the brain, were treated with IFN- . The immediate results were quite dramatic, with the disease progression stopping within 1-2 days and improvement beginning after 4-5 days of therapy. In the adult, who was severely paralyzed and receiving assisted ventilation, dramatic improvement occurred within 48 hours, followed later by gradual recovery (6).

Varicella transverse myelitis

An adult with varicella developed a clinical picture of progressive transverse myelitis. Following a few days of IFN- treatment recovery began and was complete within a few weeks.

Laryngeal papillomatosis

A 2-year-old child with severe recurrent laryngeal papillomatosis had undergone 18 operations for removal of recurrent papillomata over a period of 9 months. Following IFN- therapy no further growth occurred and the child recovered completely after 10 months of injections. A six-year follow-up showed no recurrence.

Subacute sclerosing panencephalitis (SSPE)

Three cases of SSPE showed no response to 2-4 weeks of IFN- therapy.

Interferon deficiency syndrome

Eighteen cases of acute progressive viral disease with seriously defective in vivo and in vitro IFN responses have been diagnosed. These include patients with acute fulminant hepatitis, progressive herpes encephalitis and terminal AIDS. Whereas these cases are invariably fatal without IFN therapy, treatment with IFN has led to reactivation of the IFN system and recovery in most cases (1).

DISCUSSION

Our clinical experience over a period of 7 years in which HuIFN- has been used in an open study for the treatment of 80 cases of acute life-threatening viral disease indicates that this therapy is safe and effective when given at a dosage level of 3×10^6 U/day, and the final results are most encouraging. Individual cases have shown dramatic responses especially in patients with acute fulminant hepatitis. Well controlled clinical trials are now needed to confirm the efficacy of IFN treatment in patients who are severely ill with viral illnesses.

A review of the literature shows that IFN therapy in man has been studied in no more than twenty different viral illnesses, and in only a few have well controlled clinical trials been attempted. In most early studies HuIFN- or HuIFN- was used, but during the last few years different recombinant IFNs have been tried. The following is a brief summary of some of the more promising results,

with final confirmation in most instances awaiting more extensive controlled clinical trials.

Herpesviruses

Of the approximately 80 herpesviruses which have been at least partially characterised, only 5 have been isolated from humans (7). Many of these herpesviruses have been shown to be sensitive to IFN in tissue culture and animal studies, and infections in humans with these viruses were among the first to be investigated in clinical trials. These viruses vary greatly in their biological properties. Some, like herpes simplex, have a wide host-cell range, multiply efficiently, and rapidly destroy the cells which they infect. Others, such as Epstein-Barr virus have a narrow host-cell range, and still others, such as cytomegalovirus seem to multiply slowly and are less destructive to cells. An ubiquitous property of herpesviruses is their capacity to remain latent in the host cell in which they multiply, and be triggered to reactivation by a variety of mechanisms. Many infections with these viruses are benign and self-limiting, but under certain circumstances, such as in the immune-compromised host, the infections may become life-threatening and lead to death of the host.

Herpes simplex virus infections (HSV): Two antigenic types of HSV have been described: HSV-1 associated chiefly with non-genital infections of the mouth, lips, eyes and central nervous system (although it may also cause genital disease), and HSV-2, most commonly associated with genital and neonatal (birth canal) infections, but may also cause oral and CNS infections. Persistent and recurrent infections may be characterized by "fever" blisters, genital herpes or dendritic corneal ulcers. Disseminated herpesvirus infections, meningoencephalitis and eczema herpeticum (Kaposi's varicelliform eruption) are usually life-threatening. Infections in immunosuppressed and cancer patients and those with immunodeficiency can be fatal and require specific antiviral treatment. It must be stressed that the earlier treatment is begun, the better the results.

Skin and mucous membrane herpetic infections: Several studies have shown that IFN given systemically or topically as an ointment

was effective in shortening the course of the disease and ameliorating symptoms (8,9).

Systemic herpetic infections: These have responded to daily Im injections of $3x10^6$ U HuIFN- although no well-controlled trials have been reported. We have used it in some immune-compromised patients who recovered rapidly from the infection.

Herpetic eye infections: Recurrent herpetic keratitis and dendritic keratitis have been treated with IFN drops alone (10) or combined with other therapies such as acyclovir ointment (11, 12), trifluorothymidine drops (13, 14) and secretory IgA (15). All these studies, and many others, have shown the superiority of these over other treatments, including more rapid healing as well as rapid disappearance of photophobia and pain.

Herpes encephalitis: Recently, acyclovir has become the accepted treatment for herpes encephalitis although in some cases Ara-A is preferred. However, in a recent study reported by us, 9 patients aged 7 months to 60 years suffering from severe herpes encephalitis (7 of whom were in coma) were treated with HuIFN- $3x10^6$ U daily Im. Six patients recovered. In cases where IFN was started 6 days or more after onset of symptoms, only 3/6 survived, whereas all three who received IFN within 4 days of onset of symptoms recovered (4). A single case report of a newborn baby who received intrathecal IFN for 6 days indicated no beneficial effect from this therapy (16).

Other HSV infections: Used prophylactically in a double-blind study, IFN injected prior to microneurosurgery of the trigeminal nerve significantly diminished the occurrence of post-operative herpes labialis as well as HSV viral shedding from the oropharynx (17). On the other hand, prophylactic IFN did not seem to have any significant effect on the development of HSV infections in patients undergoing renal transplantation (18).

Genital herpes infection: This is usually due to HSV-2, and is probably the commonest cause of genital ulceration in females and males. Of great clinical importance is the fact that a large group of these patients tend to have recurrent or chronic infections which often give rise to severe clinical and psychological problems.

Acyclovir ointment has been used successfully in treating the acute episodes. However the infections tend to recur, and in some cases are markedly disabling. HuIFN- and have been used topically as an ointment in uncontrolled studies and the results reported as highly significant (9).

Varicella-zoster (VZ) infections: VZ belongs to the herpes group of viruses and is a common, usually benign skin infection of children and adults. Zoster, which is common in adults, is a re-activation of latent VZ virus and is characterised by localized crops of varicella-like lesions along the course of the sensory nerve distribution of dorsal root ganglia or extramedullary ganglia of cranial nerves. In general, both chickenpox and herpes zoster (HZ) are characterised by negligible mortality but are relatively irritating, particularly with regards to itching, pain and loss of time from school or work. HZ in particular may be followed by neurologic pains lasting weeks to years, and this may cause severe disability. However, in the immunosuppressed patient, whether due to cancer or following therapy, HZ and varicella viruses tend to multiply in the viscera and disseminate and lead to more severe illness which may end fatally in 10% of cases. In these patients, IFN therapy has proved useful in well-controlled studies (19,20) as well as in our own open study. Pain is rapidly reduced in most cases, and the appearance of new vesicles suppressed. Post-neuralgic pain is less common in IFN-treated patients (19). In our experience a dose of $3x10^6$ U HuIFN- Im daily for 3-5 days, has proved sufficient in most cases that we have treated. Larger doses may be more effective, but increases the chances of toxicity. IFN-based ointments seem to be useful for controlling localised pain and pruritis. Ara-A and acyclovir also have beneficial effects in VZ infections, the latter being somewhat better (21).

The Epstein-Barr virus (EBV): The EBV was discovered in 1960 and has been shown to cause a wide spectrum of illnesses in children and adults, from a mildly contagious, self-limited febrile illness with lymphoid hyperplasia called infectious mononucleosis, to prolonged chronic illness. It is also associated with certain neoplastic diseases such as Burkitt's lymphoma and naso-pharyngeal

carcinoma. Like other viruses of the herpes group, EBV can be fatal if it occurs in the immune-compromised host. Very limited experience has been reported on the use of IFN in EBV infections, where in general, the mildness of the illness does not warrant systemic therapy. In one study of EBV infections occurring in renal transplant recipients, IFN appeared to decrease virus excretion when compared to patients receiving antithymocyte globulin or placebo (22). A trial of its use in chronic EBV infections seems warranted particularly in the light of several reports suggesting some beneficial effects and even cure in nasopharyngeal carcinoma (23).

Cytomegalovirus (CMV): CMV is an ubiquitous virus with host interactions ranging over a large spectrum of health and illness. Virus shedding from the genital tract is common in asymptomatic women, and infection of the newborn at birth is not unusual. Clinical symptomology occurs only in a small proportion of these infected infants. However fulminant CMV infections can be alarming and life-threatening. Postnatal infections also occur, apparently by contact with infected secretions or even from contaminated breast milk. In older individuals, infection can occur from blood transfusions and bone marrow and organ transplants from infected donors (24).

Although experimental studies have indicated that IFN may diminish virus excretion in chronic excretors and delay CMV reactivation in transplant recipients (25), its use therapeutically in patients with generalised CMV infection or immunosuppressed patients (such as post bone-marrow transplantation) has been generally unsatisfactory. High doses of IFN, as well as combination therapy with acyclovir or Ara-A, has given rise to unacceptable toxic sequelae. One encouraging report (25) showed that $3x10^6$ U IFN- given prophylactically before and after renal transplantation ($1x10^8$ U over a period of about 4 months), markedly reduced clinical signs of CMV infection compared to a placebo control group. Opportunistic infections with aspergillus and pneumocystis carinii were only seen in the placebo group. Further experience using combination therapies is required in order to validate whether there is a place for IFN in the treatment of CMV infections, although a combination study with acyclovir appeared to be ineffective and quite toxic (26).

IFN has been used in chronic CMV infections, again with little success. Viral shedding can be diminished, but in most cases there is no apparent effect on the clinical illness. In one of our cases with severe congenital CMV infection and immunodeficiency treated with HuIFN- for 1 month, all clinical symptoms regressed, the grossly enlarged liver returned to normal, immunological abnormalities disappeared and the child was well and normal for 1.5 years, when he suddenly went into unexplained coma and died within 2 days. Autopsy was refused.

Vaccinia

Vaccinia, a poxvirus, has been used to virtually eradicate smallpox from the face of the earth. For this reason, since 1977 smallpox vaccination has been stopped and vaccine is no longer being produced. Serious complications of vaccinia such as eczema vaccinatum, progressive vaccinia in the immune-compromised host and vaccinia gangrenosum are all conditions that require treatment. Early clinical and animal studies showed that IFN had a beneficial effect in vaccinia infection when given systemically or locally (eye drops or ointment), but well-controlled trials are lacking. More recently a live recombinant vaccinia virus has been used in an attempt to prevent this infection in patients at risk.

Respiratory virus infections

Upper respiratory illnesses caused by viruses have the highest morbidity of all infections. Discomfort and sometimes "misery" lasting several days is the classic clinical pattern seen in the majority of patients with the common cold which is caused by a broad spectrum of viruses of which the rhinoviruses and coronaviruses are probably the most common. Influenza, parainfluenza and respiratory syncytial virus (RSV) may cause more severe illness when they involve the middle or lower respiratory tract, and RSV is the commonest cause of a severe, sometimes fatal illness of the bronchi and bronchioli affecting infants below the age of 1 year.

Numerous well-controlled studies of IFN- (natural and recombinant) used mainly as an aerosol spray of the upper respiratory tract

or as nasal drops, have shown that in general this treatment is effective in partially preventing the spread of colds in households, schools or places of work if used according to a specific schedule. In a recently reported study in which household contacts of an infected individual were given INF as a spray once a day for 7 days beginning within 48 hours of onset of the illness, effectiveness in preventing colds was only 39%. However, in laboratory-exposed rhinovirus-infected volunteers the efficacy of IFN sprays was 88% as compared to placebo (27). Other studies showed that this treatment significantly reduced the duration and quantity of viral shedding, although neither spray (3x daily)or drops prevented rhinovirus infection or colds when given 28 hours after rhinovirus inocculation (28). Similar results have been reported from a double-blind placebo-controlled study in Australia (29). Another study suggested that intranasal lymphoblastoid IFN was less effective as prophylaxis against influenza A virus infections than against rhinovirus (30). However, one disconcerting effect of nasal spray or drops was the frequent occurrence of nasal irritation sometimes manifested by blood-tinged nasal mucus and superficial erosions of the nasal mucosa. This was also seen in a smaller percentage of patients receiving placebo sprays or drops.

It appears from a review of the large number of reported studies that IFN aerosol therapy will reduce remarkably the incidence of the common cold when used prophylactically. The best results were seen if the IFN was given early, although varying results were seen depending on the type and dosage of IFN used. However, aerosol sprays or drops used as symptomatic therapy for colds were not as effective although duration of viral shedding and nasal mucus production were often significantly reduced. Best results were seen in rhinovirus infections and less so with other virus infections. Further studies using modified recombinant IFNs appear to be promising in that nasal irritation is less common.

Papilloma viruses

Human papilloma viruses (HPV) are among a small group of viruses known to cause tumors in man. In general they cause benign papillomas

or warts of the skin or mucous membranes including those of the genitalia and respiratory tract because of a fastidious selectivity for squamous epithelial cells. Under certain circumstances malignancies may develop, and HPV has been identified in cervical dysplasia and in invasive cancers of the cervix.

Laryngeal papillomatosis: In this condition papillomata growing on the larynx tend to block the airway to the lungs leading to a life-threatening condition. Accepted therapy has been surgical removal or resection by lasers. However the tumors tend to regrow, sometimes rapidly, necessitating repeated operations, as occurred in our case who required 18 operations in 9 months. In older patients the growths may stop after a while leading only to voice changes. Systemic IFN has been shown to be very effective in preventing regrowth of papillomata after removal. However treatment needs to be carried on for 6-12 months or longer, and in at least 50% of patients recurrent growth occurs when treatment is stopped. Retreatment will again inhibit growth and complete remission has been seen in about 30% of juvenile-onset laryngeal papillomatosis treated with IFN- (but not with IFN-), and in almost all cases of adult-onset type (31). Another 46% had a decrease in lesion size, with responses generally occurring within 2 months, and with prolonged therapy 90% could be maintained relatively symptom-free with minimum intervention. Recommended dosage is $3x10^6$ U IFN- Im daily for 1-2 weeks (or 70,000 U/kgm for small infants), then every other day or 3 times a week for 6-12 months. With this dose side effects are minimal.

Respiratory papillomatosis: Recurrent papillomatosis of the respiratory tract is commoner in adults than in children. IFN- has been shown to lead to a moderate or better response in the majority of patients receiving therapy over a period of at least 8 months (32).

Condyloma acuminata (genital warts): A common manifestation of sexually-transmitted papillomavirus involving the vulva, vagina or perianal regions (and the penis in the male) is a typical raised condyloma which can grow to the size of a fist. Many cases will get better with the simplest of treatment. However some cases remain resistant to all therapies including surgical and laser treatments, and these may benefit from either local IFN ointment treatment, systemic

IFN therapy or injection of IFN into the base of the condyloma (33). In one study using lymphoblastoid IFN, 33% of podophyllin-resistant cases were completely cured with 1-3x10^6 U 3x weekly for 6 weeks, and an additional 30% showed partial clearance, a total response rate of 88%. (34). Intramuscular IFN- was effective in clearing up mild primary lesions in 80% of cases treated (35). Intralesional injections of IFN- cured 5 or 8 patients, male and female (33). IFN-based ointments used 4-5x daily have also proved effective in some cases.

Cutaneous warts: These have been treated either with local injection into the base of the lesion or by systemic injections of IFN. Reports, mainly from Japan, indicate an 80% or better cure rate following intralesional injection of IFN. For multiple generalised cutaneous warts, systemic IFN has been used with limited success although improvement has been noted in some cases. It should be noted that spontaneous regression of warts may occur in as many as 2/3 of children within 2 years of onset. Therefore intralesional IFN treatment may be indicated in only the severest of cases, usually in cases with a single lesion or a few annoying ones. Dosage should be at least 1-10^5 U per lesion once or twice a week for several weeks. In rare cases, a single injection may suffice.

Enteroviruses

Very little has been published on the possible benefit of IFN therapy on infections caused by this group of viruses which include poliomyelitis, coxsackie viruses A+B (herpangina, pleurodynia and foot and mouth disease) and the large group of echoviruses. Most illnesses are transient, mild and non-fatal. However, myocarditis due to coxsackie B, enteroviral meningoencephalitis and poliovirus infections may end fatally. There is no specific antiviral treatment available for these conditions and the only report of the use of IFN for treating illnesses due to any of these viruses is the one we published in 1984 in which two cases of progressively ascending bulbar poliomyelitis received HuIFN- . Both cases responded remarkably in that progress of the disease was halted dramatically and regression began within 2-3 days of onset of therapy (6). It is felt that early treatment of severe progressive enteroviral infections with IFN may

have beneficial results.

Measles

Measles is due to an infection with a paramyxovirus and is characterised by infection of the upper respiratory tract which is highly contagious. Serious complications involving the lungs and central nervous system with occasional fatalities occur in a small minority of cases. Immunization has all but eliminated this disease in developed countries, but in some underdeveloped countries measles takes a large toll especially in malnourished infants. Measles in the immune-suppressed patient can be very severe and even fatal. We have treated four very severe cases of measles including one with meningo-encephalitis with IFN- , three of whom recovered rapidly. One infant died on the 6th day with overwhelming pneumonia. The recommended dose of IFN- is 70,000-100,000 U/Kg Im daily.

Subacute sclerosing panencephalitis (SSPE): SSPE can be considered a late complication of measles with the features of a slow-growing viral infection. Electron-microscopic and serological studies suggest that the cause of the brain pathology is a defective variant of the virus. Several reports describing the use of intravenous, intramuscular and intrathecal IFN therapy in at least 14 patients showed no evidence of any therapeutic effect in any of the cases (36, 37). However in one other single case there was remarkable improvement with IFN therapy (38). Spontaneous improvement of clinical signs and symptoms is well known in this disease, so this single anecdotal report should be considered with caution.

Japanese encephalitis (JE):

JE is an endemic disease in southeast Asia affecting mainly children and is one of the more serious anthropod-borne viral infections caused by a flavivirus and characterised clinically by fever and CNS involvement leading to convulsions, paralysis, coma and death in about 20-30% of cases. Up to 50% of those that survive have permanent cerebral sequelae. Laboratory studies in Thailand showed that flavivirus causing JE and dengue hemorrhagic fever were sensitive to IFN- and IFN- . In a preliminary report, 2/4 comatose children with

JE who were treated with IFN- recovered (Prof. C. Harinasuta, personal communication). The authors suggested further studies be undertaken with both IFN- and IFN- given Iv and intrathecally.

Rabies

In animal studies IFN has been shown to provide protection against challenge by rabies virus only when it is administered before or shortly after virus challenge. Therefore the early use of IFN in rabies seems justifiable. Once clinical symptoms are present the disease is uniformly fatal and no treatment has proved of any use. In a report of 5 cases treated with IFN after symptoms appeared in another single-case report, none survived (39). It would seem appropriate to try IFN early in the incubation or prodromal stage of suspected rabies together with anti-rabies vaccine and immunoglobulin.

Acquired immune deficiency syndrome (AIDS)

This recently described disease has been shown to be due to a cytopathic retrovirus called the Human Immunodeficiency virus (HIV). Infection with this and related viruses is at present spreading at an alarming rate throughout the world by sexual dissemination in homosexuals and to a lesser degree in heterosexuals, as well as in intravenous drug users. Congenital infections of infants of infected mothers is being more commonly seen. At the time of writing this report, several agents appear to have promising anti-HIV activity in vitro. However, no particular one has been shown to have therapeutic value in well controlled trials. IFN has been used in numerous clinical studies, but as yet no definite conclusions have been drawn as to its efficacy in AIDS. In certain terminal cases of AIDS the body's IFN system has been shown to be completely defective (40), and at this stage IFN may prove useful in helping to combat secondary viral infections and prolonging life.

An unusual skin tumor called Kaposi's sarcoma commonly develops in AIDS patients. This may be accompanied by systemic symptomatology, and intercurrent and opportunistic infections are common due to the accompanying immunodeficiency. IFN- in high doses, which often leads to signs of toxicity, has been shown to lead to complete recovery in

some cases and partial remissions in others. Low dosage schedules were usually ineffective as was treatment with IFN- . In general, some patients responded well to therapy, others only partially, and some failed to derive any benefit whatsoever. Intercurrent CMV and EBV infections do not appear to be affected by the IFN therapy, although opportunistic infections occurred less frequently in treated cases. Many studies are now in progress to determine the most appropriate type of IFN to use and the best dosage schedule. The use of IFN together with an immune-stimulant has also been suggested.

Rubella virus infection

Postnatally-acquired rubella infections are usually very mild, induce immunity and do not require any treatment. Rubella rarely may infect the brain giving rise to encephalitis, and even here complete recovery is the usual course. Of more importance is congenital rubella acquired by the fetus during pregnancy, and which leads to a high incidence of congenital malformations. A rubella syndrome is sometimes seen in newborns with involvement of the brain, liver, lungs and other organs. Petechiae are common and the clinical picture is similar to that seen in congenital CMV infections. A 14-month-old baby with this syndrome complicated by vasculitis was treated for 2 weeks with $3x10^6$ U IFN- /day, and all signs and symptoms cleared up rapidly although virus secretion in the urine continued and anti-rubella IgM antibodies persisted (41).

Juvenile diabetes mellitus

For many years there has been speculation that a virus may be involved in the onset of insulin-dependent diabetes mellitus in children, and a coxsackie B4 virus has been isolated from the pancreas of a patient who died from diabetic ketoacidosis (42). Our studies showed that at the time of onset of newly-diagnosed cases of juvenile diabetes the IFN system is often activated as is seen with viral infections (43). However, IFN treatment in 2 newly diagnosed cases failed to arrest the diabetes (44).

Accidental laboratory infections - ebola virus

A laboratory worker was accidentally infected whilst processing material from African patients with hemorrhagic fever. The patient developed a disease resembling Marburg disease, and a virus similar to but serologically distinct from Marburg virus was isolated. The patient received 14 days therapy with $6x10^6$ IFN- daily as well as convalescent serum and recovered following a relatively mild course. The role of IFN in this case is difficult to judge. This report suggests that IFN may be useful in early prophylactic treatment of accidentally infected persons with unknown or unusual viruses (45).

Adenovirus

Adenovirus infections of the respiratory tract are usually mild and do not require any specific therapy. However, rare cases of fatal pneumonia or bronchiolitis obliterans as well as meningo-encephalitis have been ascribed to adenovirus infections, and may prove responsive to IFN therapy if given early in the course of the disease. Adenovirus infections of the eyes may lead to keratoconjunctivitis which may be very irritating and even disabling. This infection often occurs in epidemics and the pain and irritation may last for several weeks. IFN- drops, $2-5x10^5$ U daily divided into 8-10 drops cured the disease within an average of 6 days compared to 22 days in a control group, and prevented the appearance of subepithelial keratitis which occurred in 57% of the controls (46). This and other studies indicated that early treatment with high dosage IFN drops is a very useful treatment.

Viral hepatitis

Viral hepatitis refers to a primary infection of the liver most commonly caused by at least 5 etiologically and immunologically distinct viruses: hepatitis A (HAV), hepatitis B (HBV), hepatitis D (HDV - probably a defective virus requiring HBV synthesis for its expression), and 2 or more non A-non B viruses. Hepatitis may also occur as a secondary infection during systemic herpes viral disease due to CMV, EBV, HS and VZ infections. Clinically, most patients with viral hepatitis have a mild to moderate illness from which they recover within a few weeks with no obvious sequelae. About 10% of cases

develop evidence of chronic disease, either chronic persistent hepatitis or chronic active hepatitis which may be symptomatic or even debilitating, and in whom the viral markers may persist for years. There is a high correlation between the prevalence of HBsAG carriers and the incidence of primary hepatocellular carcinoma. Rarely, cases of acute hepatitis may progress uninhibited with the development of an acute fulminant picture of liver failure and encephalopathy. We have shown that in acute progressive and/or fulminant hepatitis, the interferon system is not as adequately activated by the viremia as it is in acute hepatitis or in most other viral infections, and in some cases these may be an absolute deficiency of the IFN response (1,3). This could possibly explain the unremitting progression of the disease in fulminant hepatitis. Treatment with exogenous IFN- reverses the process in many cases, and the IFN response usually returns to normal in patients that survive.

Acute hepatitis: Very few studies have been reported of the use of IFN in the treatment of acute viral hepatitis, particularly because of the benign nature of the majority of cases. However, because of the dangers of the development of chronic hepatitis with persistent antigenemia it seems reasonable to consider a controlled study of early treatment of acute viral hepatitis with IFN in order to prevent the complications mentioned above.

Once a hepatitis patient follows a downhill course with the development of encephalopathy the need for some specific treatment becomes urgent. As reported above, we have treated some 30 patients with progressive and fulminant hepatitis (HAV, HBV, non A-non B and herpes) with HuIFN- . Most patients were unfortunately referred for IFN treatment very late in the course of the disease when they were already in stage IV coma and when all other treatments, including acyclovir and Ara-A had proved of no use. Despite this, 59% survived. Of the patients in grade III-IV coma when IFN therapy was begun 10/21 (48%) recovered. The prognosis was poorest in patients under 4 years where only 2/8 (25%) recovered. Of the older patients 77% recovered.

These results, although based on an uncontrolled, highly biased (towards severity as the patients were usually entered into the

study as a last resort) open trial are encouraging, especially as the survival rate in fulminant hepatitis in historical controls is between 20-30% in adults, and about 10% in small infants. The usual dosage of HuIFN- was $3x10^6$ U Im per day for an average of 10 days. When a positive response was seen, it usually began on the 4th or 5th day at the same time that an antiviral state developed in the peripheral blood mononuclear cells (3). It is likely that these results could be improved upon if patients with progressive disease would be treated earlier. Obviously, confirmation of these results are required from a well-controlled double-blind study. In a study from Italy where IFN- was used no effect on the prognosis of acute fulminant hepatitis was noted (47).

SUMMARY AND SCOPE

IFN has been shown to effectively help combat a variety of viral infections. It seems to have been more effective in controlled laboratory infections or in animal studies than in clinical human trials, possibly because we have not yet overcome the problems of treating the patient as a whole with the numerous interrelating immune mechanisms involved in viral infections. It appears that it may not be sufficient to prevent viral replication with IFN, but also necessary to stimulate effective defense and tissue repairing mechanisms which will allow the body to recover with a minimal of irreversible damage. For this reason, it is possible that although certain viruses are effected by IFN in vitro, they are less responsive in vivo.

The viruses which seem most responsive to IFN therapy are the herpes group of viruses, some respiratory viruses, papillomaviruses, hepatitis viruses, measles and possibly enteroviruses. Moderately to severly ill patients with infections due to these viruses should be offered treatment with IFN, preferably HuIFN- , particularly where no effective alternative therapy is available. At the dosages recommended ($3x10^6$ U/day Im) IFN- is well tolerated, toxicity is minimal and clinical response is often seen within a few days. However, at this stage it appears that many more well controlled clinical

trials are necessary before IFN antiviral therapy can be placed on a sounder footing.

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