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Clinical uses of interferons

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Interferons were first described by Isaacs & Lindenmann working at the National Institute for Medical Research, Mill Hill in 1957 [1]. Thus, the fiftieth year of their discovery is being celebrated this year at Oxford in a meeting of the International Society for Interferon and Cytokine Research. This then is an appropriate time to review the clinical applications of the interferons. To accomplish this coherently it is necessary also to review briefly what led to the discovery of interferons, why their clinical applications were so slow in coming, and the impact of interferon research on the biomedical sciences.

Early clinical studies

The discovery of interferons was a result of research by Isaacs & Lindenmann in the field of viral interference [2], the ability of an active or inactivated virus to interfere with the growth of an unrelated virus. Until 1957, viral interference had been considered to be due directly to the action of one virus on the pathologic activity of a second agent. The Mill Hill group demonstrated that most instances of viral interference were a result of the induction by the interfering agent of cellular products, interferons, later shown to be proteins that in turn activate a number of genes responsible for the biologic effects ascribed to the interferons in addition to their antiviral activity. These include significant anti-angiogenic, cell growth inhibitory, and immunoregulatory activities [3]. Interferons play an important role in the innate immune response to virus infections [4]. Antibody to interferon exacerbates many viral diseases [5], and many viruses have developed mechanisms specifically to counteract the production or the antiviral activity of interferons [6]. Soon after their discovery, it was the antiviral activity of interferons that attracted wide interest; it was expected that they would rapidly be developed as agents to treat a variety of viral infections. This did not come to pass for several reasons.

The first road block in their clinical application was the finding that the interferons were species specific in their biological activity [7]. With a few rare exceptions, only human or primate interferons are active in human cells, so the single source of interferons for human use in the 1960s and 70s seemed to be primate cells, and the expertise necessary to exploit this source was then lacking. Furthermore, there was at first little understanding of the biophysical properties of interferons. When it was discovered that they possessed almost unprecedented biological activity, it became evident that the existing stocks of interferons with very significant antiviral activity actually were quite impure and contained very little interferon. Because of this impurity, it was impossible to accept any biological activity of an interferon preparation, other than antiviral activity, as being due to its interferon content. Also, although there was originally thought to be only one type of interferon, it was discovered that there were three important species of human interferons, each with individual properties, but all having antiviral activity. One type, interferon α (IFN-α), is produced by leucocytes, specifically by macrophages and dendritic cells. There are 13 human genes for IFN-α. A second class, interferon β (IFN-β), is produced by fibroblasts; there is only one human IFN-β gene. The genes for both IFN-α and -β are located on human chromosome 9, and have many properties in common. Thus, they are classified as type I interferons. The third principal form of interferon is termed interferon γ (IFN-γ), produced by T-cell lymphocytes. There is also only one human gene for this interferon, located on chromosome 12. IFN-γ differs in many properties from the type I interferons, and is termed a type II interferon [3]. While IFN-γ is very important in immune responses, it has not, as yet, been used clinically to any great extent [8].

Because of the excitement first generated by the discovery of interferons, there were early clinical trials of their antiviral activity involving, for the most part, the ability of a

type I monkey interferon to inhibit the development of vaccinia virus lesions in skin, or respiratory infections following exposure of volunteers to common cold viruses [9, 10]. The results of both types of studies were unimpressive, undoubtedly because of the small quantities of impure interferon available; consequently, for years studies on interferons were limited to experiments in tissue culture and attempts to produce and purify sufficient quantities of type I interferon from human white blood cells to carry out significant clinical studies, so that in the early 1970s, interferons languished in a scientific Siberia of sorts.

Interest in the possible clinical application of interferons picked up in the mid-1970s when sufficient quantities of human IFN-α became available for small studies, due in great part to the efforts of Cantell and his coworkers, who were responsible for blood banking in Finland, and had previously carried out research on interferons [11]. Purified (but not pure) preparations of human IFN-α, obtained from the white blood cells (buffy coat) of donated blood, were supplied by Cantell's group for a number of clinical experiments, many of which had promising, if not highly significant results in studies on the prevention of common colds [12] and the treatment of several herpes virus infections, such as herpes keratoconjunctivitis and varicella-zoster infections, shingles and chicken-pox [13, 14]. When treatment with interferon in tissue culture was found to inhibit chronic infections with mouse leukaemia viruses [15], it seemed reasonable to try to treat chronic virus infections in patients with interferons, and indeed clinical studies employing IFN-α in chronic hepatitis B virus (HBV) infections yielded very promising results [16]. In 1982 Jacobs *et al*. treated 10 multiple sclerosis (MS) patients with partially purified human IFN-β, administered by lumbar puncture, and reported a significant decrease in the frequency of the periodic exacerbations characteristic of MS [17].

What really revived interest in the possible clinical use of interferons, however, were limited trials, most of which employed interferon supplied by Cantell's laboratory, for the treatment of some human tumours, most notably renal cancers [18], malignant melanomas [19], lymphomas, and leukaemias [20]. These clinical studies were a rational follow up to a number of reports that type I interferons were effective in treating cancers in mice [21]. Interest in interferons as a treatment of cancers was greatly stimulated by a report from Sweden that osteosarcomas responded to treatment with IFN-α, a study that subsequently was shown to be flawed [22]. On the basis of this paper, however, a workshop, involving almost all scientists then involved in interferon research, took place in 1975 (ironically, on April 1) at Memorial Sloan-Kettering Cancer Center in New York City [23]. Reports of this meeting had both positive and negative consequences. The notion that interferons might be important anticancer drugs led to widespread, unwarranted expectations of them being a general cure for cancer. On the positive side, however, interest in finding better sources for a potential wonder drug, led directly to the cloning of genes for IFN-α, which were among the first human genes to be cloned [24]. Later, the genes for IFN-β and -γ were also cloned [25, 26]. The production of quantities of interferon sufficient to carry out clinical trials with significant results was then possible, which led to some clarification of what the role of interferons might be in the treatment of human diseases.

Clinical studies with recombinant interferons

Antiviral activity

Recombinant IFN-α forms are widely employed with some success in the treatment of chronic HBV and hepatitis C virus (HVC) infections and some forms of cancer. IFN-β treatment for MS is regularly used to limit exacerbations of MS. IFN-γ has been approved for clinical use only in a rare congenital disorder, chronic granulomatous disease.

By far the best understood application of any clinically useful interferon is against chronic HCV infections, for which IFN-α has been an approved treatment since 1991 [27]. HCV is a widespread infection caused by contaminated blood products or drug injection with contaminated needles. Although modern blood bank technology has almost eliminated the former, the latter remains a major problem. There are millions of HCV-infected patients worldwide. The progress of HCV infections is insidious, often not being clinically manifest for two or three decades after initial infection with the virus. Chronic HCV infection may cause serious hepatic malfunction which eventually results in cirrhosis of the liver and in life-threatening oesophageal varices. A small percentage of HCV patients eventually develop hepatocellular cancers (hepatomas). Infections with HBV and HCV are a significant cause of death in patients with AIDS.

HCV is a small ribovirus with six genotypes, of which genotype 1, unfortunately the most common infection in North America, is relatively insensitive to IFN-α. The resistance to IFN resides in a nonstructural viral protein, a serine protease that inactivates the signal leading to interferon production, thus facilitating the development of a chronic infection with HCV [28]. In order to augment the effectiveness of IFN-α employed in the treatment of HCV, two alterations in the treatment protocol for the infection were initiated. Ribavirin, an oral nucleoside analogue was added to the regimen, and the IFN-α was conjugated to polyethylene glycol (peginterferon), thus decreasing its renal clearance and significantly increasing its half-life from about 5 h to almost 90 h. With the combined ribavirin/peginterferon treatment more than 75% of nongenotype 1 HCV patients maintain a sustained anti-HCV response, while up to 50% of the patients infected with the genotype 1 HCV respond to this combined treatment. In those patients responding to peginterferon/ribavirin therapy, virus-induced liver damage fails to progress and some

degree of healing takes place. Unfortunately, the prolonged peginterferon therapy necessary to control chronic HCV or HBV infections is often associated with serious side-effects such fever, depression, and muscle pain [27].

Chronic HBV infection is the other major antiviral application of interferons [29]. HBV is a hepatotropic DNA virus. Like HCV, HBV infection is associated with contaminated blood or blood products, but unlike HCV is also commonly a sexually transmitted disease. An effective vaccine for HBV has greatly decreased the incidence of this disease, but a large number of those chronically infected remains worldwide. At present, chronic infections with HBV are treated with a combination of peginterferon and one of several nucleotide analogues that inhibit the replication of the HBV genome such as lamivudine, adefovir, entecavir, or tenofovir. New, more effective anti-HBV nucleotide analogues are under development. With peginterferon/lamivudine therapy, about 60% of patients demonstrate a significant anti-HBV response, which is more effective than therapy with either treatment alone [30].

IFN-α is also employed in the treatment of infection caused by human herpes virus-8, the aetiological agent in Kaposi's sarcoma (KS), formerly a rare form of cancer that has become prominent because of it association with AIDS [31]. KS is a mutifocal tumour of the vascular endothelium, the most frequent manifestation of which is the development of multiple purple skin nodules. HHV-8 propagates in AIDS patients due to the suppression of the immune response associated with their disease. In addition, HHV-8 produces a protein that directly inhibits interferon induction. Since KS is caused by a virus, it was logical to attempt to treat the disease with IFN-α. This treatment can be local, directly applied to skin lesions, or systemic [32]. The success rate approaches 60% when the therapy with IFN-α is combined with effective antiretroviral treatment for AIDS. A few other human tumours which are caused by infection with members of the human papillomatosis virus (HPV) group have been treated with interferons. These include recurrent respiratory papillomatosis [33] and genital warts [34]. Juvenile laryngeal papillomatosis, which can be a life threatening disease, has been treated with IFN-α for over 20 years [35]. Such treatment is effective in infections with HPV types that have a low potential for inducing malignant transformation, but survival of patients is poor in infections with types with a high rate of cancer induction. Genital warts, too, are induced by HPV infections, and may be treated by interferons. However, a number of less expensive forms of therapy are also available for this disease so that interferons are no longer recommended as its primary mode of treatment [34].

Antitumour activity

Because of their cell differentiation and growth regulatory properties, interferons have been used in attempts to treat neoplasms. Several forms of haematological cancers and solid tumours have been treated with interferons with some success. However, as little as is known of the mechanism of antiviral actions of interferons, there is even less understood about their effectiveness, such as it is, in cancer therapy. Even before recombinant interferons were available, remissions were reported with partially purified IFN-α in patients with hairy-cell leukaemia [36], usually a slowly progressive, rare form of B-cell leukaemia. Some success was also reported with treatment of chronic myelogenous leukaemia, a more common B-cell form of the disease [37]. In both of these forms of leukaemia, however, more effective forms of therapy have been devised through our rapidly developing understanding of the molecular mechanisms involved in the genesis and progression of some forms of cancer, so that interferons are no longer employed as first-line therapies in the treatment of these leukaemias [38].

There are two forms of cancer for which interferons are still commonly employed as therapy, mainly because no alternative treatment has been found. About 15% of metastatic renal-cell carcinomas respond to treatment with IFN-α alone. However, when employed in the treatment of this form of cancer, IFN-α is used in conjunction with other forms of biological response modifiers such as interleukin-2. Recently, as in the case of chronic myelogenous leukaemia and hairy cell leukaemia treatment, more effective forms of therapy for renal-cell cancers than interferons are now available [39].

The other major cancer for which interferon treatment is employed as adjuvant therapy is for cutaneous melanoma that has metastasized to local lymph nodes [40]. Malignant melanomas are probably the most capricious form of cancer, so that it is difficult to evaluate how effective any therapy directed at them is. A number of reports show improved survival, a decreased rate of relapse, and an improved quality life in melanoma patients treated with high dosages of IFN-α. Because of the toxicity associated with prolonged, high doses of interferon, a number of European studies of lower doses of interferon were undertaken. However, none of the low dosage regimens has so far been associated with a significant recurrence-free patient survival.

The anti-angiogenic property of interferons has been employed for the treatment of very large, life-threatening haemangiomas (benign tumours of blood vessels) in infants. These haemangiomas usually respond to corticosteroid therapy. However, where this treatment has been ineffective, IFN-α therapy for several weeks or months has been life-saving in cases where steroids have failed [41].

Treatment of multiple sclerosis (MS)

MS is a relentlessly progressive neurodegenerative disease, the course of which usually features a series of remissions and relapses. MS is associated with demyelination of nerves. Treatment of MS with IFN-β was initiated based on the immunomodulatory properties of the interferons [41]. Because of the unpredictable course of MS,

judging the effectiveness of any form of therapy for this disease has been difficult. However, well-controlled studies have demonstrated that intramuscular treatment with IFN-β results in a reduction in the annual rate of relapses of MS. Initiation of IFN-β treatment with the first instance of demyelination in MS, appears to be a justified therapeutic intervention [42]. Addition of natalizumab, a recombinant monoclonal antibody to an integrin, augments the ability of IFN-β to decrease the rate of MS progression. Employed together, natalizumab and IFN-β treatment results in about a 50% reduction in the rate of MS relapses, when compared with that observed with IFN-β alone [43].

It would be remiss to discuss the clinical uses of interferons and not to mention in passing the profound effect their discovery has had on the biomedical sciences. As discussed above, they were among the first proteins to be cloned, and so research on them has contributed significantly to the rapid development of molecular biology. The interferons are now considered to be members of the cytokine and growth factor class of biologically active agents. Because research on interferons had been initiated well before the other members of the cytokine and growth factor group were discovered, interferons were seminal in the development of this important field.

As may be evident from this brief description of the therapeutic applications of the interferons, there is very little understanding of the mechanisms of almost all of the medically important applications of the interferons. A greater insight into how interferons bring about these clinically useful activities may well lead to the development of pharmacologically active agents which are more specific and potent in their biological effects than are the interferons themselves.

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