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Progress in the development and use of antiviral drugs and interferon

Report of a
WHO Scientific Group

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AND USE OF ANTIVIRAL DRUGS AND INTERFERON

Geneva, 10-13 March 1987

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PROGRESS IN THE DEVELOPMENT AND USE OF ANTIVIRAL DRUGS AND INTERFERON

Report of a WHO Scientific Group

A WHO Scientific Group met in Geneva from 10 to 13 March 1987. The meeting was opened on behalf of the Director-General by Dr G. Torrigiani, Chief, Microbiology and Immunology Support Services.

Dr Torrigiani explained that the Scientific Group had been convened because, in recent years, much new information had been published on antiviral agents and because, unfortunately, new problems had arisen with some drugs, such as undesirable side-effects, an influence on the immune system, or the appearance of drug-resistant mutants of viruses.

The Group was expected to review the results of recent studies of antiviral drugs and interferons, to identify the types of virus infection requiring antiviral drug treatment, and to discuss the most appropriate use of antiviral agents, in order to make recommendations to the World Health Organization on the development and application of these products, including recommendations on the directions for future research, the surveillance of drug-resistant strains of viruses, and on drug-testing systems.

1. INTRODUCTION

The development of antiviral agents for the treatment of infectious viral diseases has progressed slowly. This is due in large part to the early belief of many virologists that agents that could inhibit viral replication would also be toxic to normal cells. In addition, there was the unsubstantiated assumption that by the time clinical symptoms become apparent, viral replication is already on the decline and the damage caused by viruses has been completed. Numerous compounds have been evaluated for antiviral activity (in cell culture and animal systems) and one of the first reported to have activity in human subjects was metisazone against smallpox. Smallpox was eventually eradicated using an effective vaccine, but

unfortunately vaccines are not available for all the viral infections of clinical importance and there is a need to develop antiviral drugs, of either synthetic or natural origin.

The discovery of interferon in 1957 encouraged hopes that specific inhibition of virus multiplication was possible. This was substantiated by the discovery in 1962 that picornavirus RNA synthesis could be selectively inhibited by benzimidazole derivatives, the first demonstration of the effects of a compound of low relative molecular mass on a virus-coded enzyme, RNA replicase.

Idoxuridine was the first drug to be approved by a national authority (in 1962) but, because of systemic toxicity, its use was restricted to the topical therapy of herpesviral infection of the eye, herpesviral keratitis, a major cause of blindness. Soon thereafter amantadine was found to be effective orally for the prophylaxis of respiratory infections due to influenza A virus. The development of antiviral drugs was given strong impetus in the mid-1970s when vidarabine was shown to be clinically effective systemically against herpesviral encephalitis—a very serious disease. The diseases with the greatest potential for benefit remain those that are dependent on continued viral replication for pathogenesis and which lend themselves to rapid viral diagnosis.

Among the topics discussed by the Scientific Group were the various approaches taken for the development and synthesis of antiviral agents, their mode of action and pharmacology, their safety and efficacy, the viral diseases for which antiviral agents are required, and the best strategies for treatment.

2. DEVELOPMENT OF ANTIVIRAL DRUGS AND INTERFERONS

2.1 Antiviral drugs

The development of antiviral drugs has to a large extent been concentrated on drugs useful in the treatment of diseases caused by the herpesviruses. Influenza and rhinovirus infections have received less attention, but have also been considered important targets for chemotherapy or prophylaxis. The treatment of acquired immunodeficiency syndrome (AIDS) with antiviral drugs has

recently become of critical importance, and there are several other virus infections for which the development of therapy is needed because of their medical severity.

A major target for antiviral drugs has been the inhibition of viral nucleic acid synthesis either by inhibition of the viral nucleic acid polymerases or by incorporation of the drug into the viral genome. Most of the inhibitors are nucleoside analogues and are often phosphorylated by viral and cellular kinases to triphosphates before acting as inhibitors. Compounds such as aciclovir are preferentially activated in the infected cell by a viral-encoded thymidine kinase.

For practical reasons, screening for antiviral activity is usually carried out in cell cultures infected with the virus. This is easy with herpesviruses, influenza viruses, and picornaviruses, but owing to the limited number of containment (P-3) laboratories the screening of compounds against human immunodeficiency virus (HIV) has been somewhat restricted. Unfortunately, there are also other viruses for which there is no easy way of screening compounds, in these cases because there are no simple cell culture assays available.

The compounds that are found to be effective in cell culture are then evaluated in experimental animals infected with the virus in question. However, animal models do not exist for some virus infections, or if they do, there may be a shortage of animals, as is the case for the animal models of HIV infection. A major problem is that an agent found to be effective in cell culture as well as in experimental animals, may for a variety of reasons not be of value in man, because of either lack of efficacy or unpredictable toxicity.

At present, serendipity still plays a major role in our search for antiviral drugs, but as our understanding of the molecular biology of viral replication and virus-host interrelationships increases it should be possible to make a more intelligent selection of compounds for screening and also perhaps to design novel compounds for specific viral targets and to correct any host defects that are elucidated.

In the near future, it should be possible to base the design of inhibitors on a knowledge of the three dimensional structure of the target site, which may be determined by X-ray crystallography or by nuclear magnetic resonance studies, and subsequent molecular modelling with computers. For example, it seems likely that the efforts to clone and determine the structure of HIV proteins will provide, in a few years' time, a molecular basis for the rational design of new inhibitors. Additional information about the structural proteins and viral enzymes could lead to the preparation of

inhibitors that affect the uncoating of structural proteins, as has been achieved recently with picornaviruses, as well as to the development of new inhibitors of viral enzymes.

The evaluation of antiviral drugs in cell cultures has shown that the type of cell, the condition of the cells, the type of assay, the virus strain, the multiplicity of infection, the presence of different metabolites, and other variables have a considerable influence on the effect of a compound on virus replication. Thus a variety of cell types, including human cells, and different multiplicities of infection should be used.

When animals infected with different viruses are used as models for evaluation of antiviral drugs, several aspects have to be carefully considered. If a compound behaves differently in animal and human cells, it indicates that the *in vivo* efficacy may also vary. The temporal course of the infection is also important. A primary herpes simplex infection in an animal has a more prolonged course than a recurrent herpes simplex infection in a human subject and therefore there is a better chance of intervening in animals with a drug that inhibits replication. It is also possible that the metabolism of a drug differs considerably in animals and human subjects. Large differences might also be expected between individuals. The pharmacokinetic properties of a drug, which affect its ability to reach the infected tissue in a sufficiently high concentration and the maintenance of this concentration at the target site for the required period of time are of fundamental importance.

More sophisticated methods of analysis are required in order to be able to quantify the drug and its metabolites at the target site in the infected cell, because, if the drug has an intracellular site of action, the cellular concentration is more important than the measured serum levels. For example, it has been reported with drugs such as aciclovir, vidarabine, and ganciclovir that a blood plasma concentration below the ED_{50} , a dose required to inhibit the virus by 50% in cell culture, can be sufficient for effective therapy of viral infections in patients.

Better drug delivery systems are important from two points of view: (a) to increase the concentration of drug at the site of viral replication, and (b) to decrease the concentration in other tissues and thus limit the potential toxicity. For practical reasons, drug delivery systems that result in slow uptake of the drug or slow release of the drug into the blood may be required. Delivery of drugs to specific tissues or areas such as the central nervous system and mucosal

membranes seems to be an important area for research and improvement.

The development of viral resistance to drugs has so far not been a great problem and has been seen only in a few patients, the majority of whom were immunocompromised. The wide-scale use of antiviral drugs in immunocompromised patients, e.g., cancer patients or individuals undergoing organ transplants who are receiving immunosuppressive drugs, may result in the more frequent occurrence of drug-resistant viruses. This may well require the development of additional antiviral compounds with different modes of action and perhaps the use of combination therapy.

As mentioned above, research to discover new targets for antiviral drugs is critical and fortunately the current status of viral molecular biology is extremely favourable for such research. The mode of action of the antiherpetic drugs currently in clinical use generally depends upon the rapid increase of viral encoded thymidine kinase in the infected cell which either traps the drug by phosphorylation or activates the drug preferentially in the infected cell.

Zidovudine¹ was first synthesized in the early sixties, and was shown later to inhibit the replication of murine retrovirus. It has been postulated that the drug is incorporated into the viral DNA as a chain terminator. The requirement of the HIV-encoded reverse transcriptase for virus replication encouraged the evaluation of zidovudine as a potential inhibitor of this retrovirus.

The development of antiviral agents to attack many other potential targets is being pursued by government agencies, universities, and pharmaceutical firms. For example, the development of polypeptides to interfere with regulatory proteins or with enzymes such as the proteases required for protein processing is a feasible approach to the inhibition of not only HIV but also other viruses of clinical importance.

Several viruses, e.g., herpesvirus, human papilloma virus, hepatitis B virus, and HIV, result in a persistent or latent infection where the virus genome is generally integrated into the cellular genome, or persists within the cell in an episomal form. This calls for increased research efforts to understand the mechanisms involved in persistent infections and latency. A better understanding of these mechanisms is likely to be necessary for the development of

¹ Sometimes referred to as AZT.

appropriate therapies. For example, knowledge of how latency is regulated within the cell may make it possible to prevent recurrences; if a specific protein is required to activate the latent viral genome, can an inhibitory polypeptide be synthesized to interfere with such activation? It will be especially important to analyse the possibilities of interfering with the persistent infections caused by HIV, human papilloma virus and hepatitis B virus.

A better understanding of the roles of virus replication and immune reactions in human disease, as well as in animal models, should help to improve the use of antiviral drugs. It is also necessary to know when and where virus replication occurs in human subjects and in animal models in order to be able to choose the most suitable drugs for clinical testing.

2.2 Interferons

Interferon (IFN) was thought at first to be a single, highly specific, non-toxic, broad-spectrum, antiviral substance. Thirty years of research have revealed that all the members of the IFN superfamily have antiviral, cytostatic, immunodulatory, and other activities. Interferons are unique among the antivirals; they induce an antiviral state in cells and inhibit the intercellular replication of most known viruses. In addition, they stimulate various host defence mechanisms to destroy virus-infected cells. The interferons thus belong to the heterogeneous group of biological response modifiers that are being increasingly used in the treatment of viral infections and malignancies.

There are at least 15 different human alpha-IFNs, at least two beta-IFNs, and one gamma-IFN. Among the different alpha-IFNs the amino acid homology is about 80%, there is some homology between the alpha- and beta-IFNs, but very little between the gamma-IFN and the others. All interferons contain about 150 amino acids. Some interferons are glycosylated, others not.

Viruses and polynucleotides induce the synthesis of alpha-IFNs in certain white cells and the synthesis of interferon-beta-1 in epithelial cells and fibroblasts. Exposure of natural killer cells to malignant or virus-infected cells stimulates the synthesis of alpha-IFNs; gamma-IFN is induced by mitogens and antigens in T lymphocytes. The newly recognized beta-2 interferon is induced in fibroblasts by a number of growth factors and it may be an important physiological regulator of cell growth.

Interferons belong to the first line of defence against viral infections and are believed to play an important role in the outcome of many viral infections. Interferons induce inflammatory reactions and they increase the cytotoxicity of macrophages, T lymphocytes, and natural killer cells. Interferons, especially gamma-IFN, seem to participate in the immune response. There is still much to be learned about the physiological roles of the interferons.

Alpha- and beta-IFNs bind to the same cell surface receptor, but a separate receptor exists for gamma-IFN. All interferons induce the synthesis of many polypeptides. The function of most of them is unknown. They include a protein kinase that affects RNA translation and a 2'5'-oligoadenylate synthetase that affects the stability of RNA. Their relationship to viral inhibition is not known yet. Interferons enhance the expression of certain antigens, e.g., HLA, at the cell surface.

The early problems with the availability of interferon have been overcome by the use of large-scale cell culture methods of production and the advent of recombinant DNA technology. At present, clinical trials are being conducted with natural alpha- and beta-IFNs and two recombinant alpha-2 interferons that differ from each other in respect of one or two amino acids. Recombinant beta interferon, in which serine has been substituted for cysteine to increase stability, as well as recombinant gamma-IFN, are also undergoing clinical trials. All recombinant preparations are derived from *Escherichia coli* and therefore are not glycosylated. Efforts are being made to enhance the beneficial properties of interferons and to decrease their adverse effects by structural modifications.

Both human leukocyte and lymphoblastoid interferons are mixtures of at least ten different alpha-subtypes, but the compositions of the two preparations are different. The alpha-IFN subtypes differ in their biological activity and may act synergistically.

Since human interferons have little or no activity in most animal species, animal studies have been hampered by the lack, or shortage, of homologous interferons. Studies are now being carried out to produce different animal interferons by recombinant DNA technology. Attempts are also being made to modify the pharmacokinetics and to improve the targeting of interferons.

All interferons cause influenza-like symptoms such as fever, chills, fatigue, headache, myalgia, and arthralgia. The first injections cause the most pronounced side-effects and the symptoms tend to decrease

on continued administration. Treatment with very high doses for a short time, or with moderate doses for a long time, affects the central nervous system. Symptoms include vertigo, lethargy, nausea, and decreased mental capacity. The side-effects are dose related, but disappear when treatment is stopped. Laboratory findings include leukopenia, thrombocytopenia, and anaemia. Elevation of the levels of liver enzymes is not uncommon. The effects on the central nervous system may be associated with electroencephalogram changes.

3. VIRAL INFECTIONS

3.1 Acute infections

3.1.1 *Herpes virus infections*

The most extensive studies on antiviral chemotherapy have involved infections by members of the herpesvirus group. The following antiviral agents are in clinical use or are being considered for the treatment of herpesvirus infections:

- idoxuridine (IDU)
- trifluridine (TFT)
- vidarabine (AraA)
- aciclovir (ACV)
- E-5-(2-bromovinyl)-2'-deoxyuridine (BVDU)
- ganciclovir
- 1-2(-deoxy-2-fluoro- β -D-arabinofuranosyl)-5-iodocytosine (FIAC)
- foscarnet sodium
- interferons
- immunoglobulins

3.1.2 *Herpetic infections of the eye*

In the developed countries, herpes simplex virus infection of the corneae (primary infections or recurrences) is quite common and is the most important infection leading to blindness. Topical treatment is feasible because of the location of the infection. Idoxuridine was first introduced in 1962 but is no longer the drug of choice for treatment of keratitis herpetica, since it may impair corneal wound

healing. Vidarabine, trifluridine, aciclovir, and BVDU have been shown to be effective in treating herpes infections of the eye; trifluridine is preferred by many ophthalmologists as the most effective drug, but it is quite expensive and not licensed in many countries.

In controlled studies interferon has proved to be inactive, whereas a combination of interferon with either trifluridine or aciclovir has been more effective than the antiviral drug alone.

3.1.3 *Herpesviral encephalitis*

This disease was lethal in about 70% of the patients in the placebo groups of controlled trials. Vidarabine was first shown to be active in a small double-blind, placebo-controlled study, and reduced the mortality in a subsequent open trial. In a subsequent comparison of aciclovir and vidarabine, aciclovir was found even better than vidarabine. In addition, aciclovir can be administered more easily than vidarabine, which is not very water-soluble and requires the infusion of large volumes of fluid. Furthermore, aciclovir is less toxic than vidarabine.

Early treatment is an important factor in determining a successful outcome. This obviously requires rapid viral diagnosis. In view of the low toxicity of aciclovir, and because of the importance of early treatment, many clinicians start treatment before a diagnosis has been established.

3.1.4 *Neonatal herpes*

In a comparative study on the effects of aciclovir and vidarabine the preliminary results indicate that both compounds are equally effective. The outcome of the disease depended on the clinical pattern: children with infections localized to the skin, eye, or mouth all survived and 85% of the vidarabine-treated and 93% of the aciclovir-treated infants were developing normally one year after infection.

Disseminated disease was most lethal (50–65% of patients) and only 23% (vidarabine) and 29% (aciclovir) were developing normally at one year. Though the proportions of children with central nervous system involvement that died were only 13% (vidarabine) and 8% (aciclovir), respectively, only 37% (vidarabine) and 34% (aciclovir) of them were developing normally at one year.

3.1.5 *Oral/genital herpes*

Treatment of primary oral/genital herpes with aciclovir has been known to speed resolution of symptoms (pain) and lesions, and to curtail virus shedding. In severe cases of primary genital herpes, intravenous administration of aciclovir appears preferable, but treatment of recurrent episodes of oral and genital herpes is of limited value. Aciclovir treatment does not seem to affect the recurrence rate in patients treated successfully for primary herpes.

Aciclovir (2–5 200-mg capsules orally per day) has been shown to be effective prophylactically in patients with frequent and severe recurrent episodes of herpes. Recurrences occur soon after treatment ceases. It has yet to be shown whether long-term treatment with aciclovir is innocuous.

Aciclovir has proved very useful and often life-saving in immunocompromised patients with herpes infections. Drug resistant mutants have been observed and this is of great concern.

3.1.6 *Varicella and zoster*

Varicella and varicella-zoster may be life-threatening in immunocompromised patients and both aciclovir and to a lesser extent vidarabine have proved effective in both diseases. Cutaneous and systemic dissemination are both reduced, as is viral shedding. Though the period of pain is also shortened in treated patients, post-herpetic neuralgia does not seem to be affected.

Among the drugs under development, BVDU and FIAC are very potent against human (alpha) herpesvirus 3, which causes zoster. Their efficacy and safety are being assessed in current clinical trials.

Early treatment of varicella and zoster with alpha interferon reduces cutaneous and visceral dissemination in immunocompromised patients. The advent of synthetic antivirals has reduced interest in the use of interferon in the therapy of these diseases, but the latter may yet find a place in combination therapy.

3.1.7 *Cytomegalovirus infections*

Vidarabine and aciclovir have little or no effect against cytomegalovirus.

The acyclic nucleoside analogue ganciclovir and foscarnet sodium appear to be effective in some types of cytomegalovirus infections in immunocompromised patients. AIDS patients with cytomegaloviral

retinitis seem to benefit from treatment with ganciclovir and foscarnet sodium but relapses are frequent and a prophylactic therapy is needed. In spite of these imperfections, such treatment is important in enhancing the patient's quality of life. The concomitant use in some patients of drugs against HIV and cytomegalovirus is a likely development. Cytomegaloviral pneumonitis in bone marrow transplant recipients seems not to have responded to ganciclovir or foscarnet sodium, while pneumonitis in less immunocompromised patients might benefit from these drugs. It remains to be seen whether the clinical benefits of these drugs will outweigh possible toxicity.

Attempts to treat cytomegalovirus infections in bone marrow transplant patients with interferon have failed, but interferon prophylaxis has some effect in preventing serious cytomegalovirus infections in seropositive renal-transplant patients.

Administration of immunoglobulins with high titres of neutralizing antibody is also believed to be of value in the treatment of cytomegalovirus infections in transplant patients.

3.1.8 *Gammaherpesviral mononucleosis*

In a controlled trial in patients with this disease, aciclovir exhibited no significant clinical effect. However, viral shedding was less in the aciclovir group.

3.1.9 *Respiratory viral infections*

The common cold. The common cold is caused mainly by rhinoviruses and is one of the major causes of morbidity and absence from work and education. Vaccination is not feasible at present owing to the large number of virus serotypes. A specific problem in antiviral chemotherapy of the common cold is the mildness of infection and the short duration of the disease. In consequence, only antivirals that are virtually free of toxicity are acceptable. Ideally, they should be available as over-the-counter drugs.

The common cold was one of the first infections on which interferon was tested. Shortage of interferon is nowadays no longer a problem. Several studies have shown that topical treatment with interferon (spray) is of no benefit in rhinovirus infections. On the other hand, some prophylactic effect of topically applied interferon

was demonstrated in volunteers subsequently infected experimentally with rhinoviruses. Further volunteer experiments gave indications of optimum dosage and timing. Interferon alpha was shown to be effective prophylactically in a family setting when topical treatment at a dose of 5×10^6 IU per day was begun within 48 hours of onset of illness in the index case.

However, interferon given in these doses for a period of more than one week has side-effects that mimic the symptoms of the common cold—nasal congestion and nasal mucosal bleeding—and, therefore, long-term prophylaxis of the common cold with interferon is not justified. Short-term postexposure prophylaxis of rhinovirus infections with intranasal interferon could be of importance for special risk groups such as asthma or chronic bronchitis sufferers. Future studies should be directed towards obtaining less toxic interferons from among the natural interferons or by means of structural modifications. Combination therapy should also be investigated as a way of improving the efficacy and decreasing the toxicity.

Various synthetic chemicals, such as 4'-dichloroflavan, 4'-ethoxy-2'-hydroxy-4,6'-dimethoxychalcone (Ro-09-0410), and the benzimidazole derivative enviroxime, though very active in inhibiting rhinovirus replication in cell culture, have proved ineffective in the treatment of patients with common colds, regardless of whether the application was systemic or topical. The reason seems to be either that the compounds are still not active enough to show systemic or local toxicity or that they do not reach the nasal epithelium.

Promising results have been obtained in controlling the transmission of rhinoviruses when tissues impregnated with an antiviral agent have been used regularly.

Influenza. Amantadine has been shown in many controlled trials to be effective against influenza A infections, both prophylactically and therapeutically (administered within 48 hours of onset of symptoms). In prophylactic trials, a 70–90% reduction has often been achieved in the number of laboratory-confirmed influenza A infections, as compared with the placebo group. In therapeutic studies, fever, symptoms, and virus shedding have been significantly reduced, and the disease has been shortened.

Rimantadine, a derivative of amantadine, has proved to be of similar clinical benefit. While amantadine often induces side-effects,

e.g., dizziness, nervousness, failure to concentrate, rimantadine seems not to produce any side-effects.

Considering the effectiveness of these drugs it is unfortunate that they are so little used in the treatment of influenza A infections.

Ribavirin has also been shown to be active against influenza A and B. Since it has to be administered by aerosol, its usefulness will probably be restricted to hospitalized patients with influenza B infections.

Respiratory syncytial virus infections. Respiratory syncytial virus is the major respiratory pathogen of infants and is responsible for severe disease involving bronchiolitis and pneumonia. Ribavirin, given by aerosol continuously for 18 hours was shown in a double-blind study to be of modest but significant clinical benefit in infants with a median age of 3–4 months who had this type of infection.

Studies with immune therapy are in progress. Simultaneous administration of ribavirin and antiserum may improve the therapeutic effects considerably as compared to treatment with either substance alone.

3.1.10 *Arenavirus, arbovirus, and other severe virus infections*

Many of the patients with severe diseases caused by infection with enveloped RNA viruses could benefit significantly from antiviral therapy. These diseases include rabies caused by a rhabdovirus, Lassa fever, Argentinian and Bolivian haemorrhagic fevers caused by arenaviruses, Ebola and Marburg haemorrhagic fevers caused by Filoviridae, other haemorrhagic fevers associated with bunyavirus infections (Crimean-Congo haemorrhagic fever (CCHF), Rift Valley fever, and haemorrhagic fever with renal syndrome (HFRS)), as well as many of the togavirus and flavivirus diseases such as Japanese encephalitis, yellow fever, and dengue fever. The status of antiviral therapy differs for each of these infections, but, in general, few clinical trials have been reported.

Many of these infections cause hundreds of thousands of cases and thousands of deaths each year and all are associated with a high case-fatality rate. For example, the case-fatality rate is nearly 100% for rabies, approximately 90% for Ebola haemorrhagic fever, and 15–20% for hospitalized Lassa fever patients.

One of the clinical successes, so far, against these viruses has been the therapy of some arenavirus infections. Human infection by Lassa virus is frequent in West Africa, the antibody prevalence being up to

50% in some villages. In two trials, the case-fatality rate was significantly reduced by ribavirin therapy. The outcome is closely related to the inhibition of viral replication. Although ribavirin is helpful at any stage of the infection, it is most effective when given in the first week; the pathogenesis of the infection appears to be less easily reversible later in the illness. Similar success has been obtained against Junin virus infection in Argentina using convalescent plasma. Patients so treated within the first week of illness had a case-fatality rate of 1% compared to 14% in untreated patients.

3.2 Chronic infections

3.2.1 Papilloma virus infections

A number of small studies indicate that long-term systemic interferon treatment of patients with laryngeal papillomatosis reduces the size of these benign but life-threatening tumours or retards the development of new lesions. Two large studies in progress with different alpha interferons support the early favourable experiences, but it is not clear how long the benefit will last.

Administration of alpha or beta interferon directly into the lesion appears to result in the resolution of genital warts in roughly 50% of patients. Additional trials are under way to evaluate both systemic treatment and the combination of interferon with other treatment modalities.

3.2.2 Chronic viral hepatitis

Hepatitis B virus, with or without hepatitis delta virus (HDV) infection, and the parenterally transmitted non-A, non-B viruses both give rise to chronic hepatitis which may progress to cirrhosis and, in the case of hepatitis B, to hepatocellular carcinoma.

During acute hepatitis B virus infection, recovery may be dependent on the early production of alpha interferon, this being followed by the lysis of infected hepatocytes by cytotoxic T lymphocytes sensitized to viral (nucleocapsid) antigens.

In some patients with chronic hepatitis B virus infection arising in adult life, partial deficiencies of production have been identified; in neonatally acquired infection, deficiencies of the immune response to nucleocapsid antigens may occur. The heterogeneity of the chronic

hepatitis B virus carrier state suggests that different approaches to therapy may be needed in these subgroups.

Both synthetic and natural antiviral compounds capable of inhibiting hepatitis B virus replication are now available and various regimens are being evaluated in controlled studies. The results of the treatment seems to depend on the integrity of the host's immune response. Spontaneous seroconversion from HBe antigen to antibody, associated with a transient exacerbation followed by long-term amelioration of the disease, occurs in 0–15% of cases per annum. Against this background, both alpha interferon (leukocyte, lymphoblastoid, and recombinant) and beta interferon given for several months in moderate doses appear to have had a significant beneficial effect in both heterosexual and homosexual carriers infected in adulthood, but not in Chinese and Japanese carriers who were probably infected at birth. Vidarabine monophosphate may also be effective in heterosexual carriers, but not in homosexual carriers or those infected at birth. Pretreatment with steroids may enhance the response to antiviral regimens.

Inhibition of viral replication, associated with HBe antigen/antibody seroconversion is usually long-lasting and accompanied, after a transient exacerbation, by amelioration of the inflammatory liver disease. Reactivation may occur, particularly in homosexual patients with or without HIV infection. If integration of hepatitis B virus sequences into the host cell genome has occurred before starting treatment, HBs-antigenaemia will continue after cessation of detectable hepatitis B virus replication. However, inflammatory liver disease will improve in these patients if long-term inhibition of hepatitis B virus replication is achieved. Patients treated early in the course of the disease will lose HBs antigen from their serum if inhibition of virus replication is achieved.

In all of the controlled studies reported so far, less than 50% of patients have undergone HBe antigen to antibody seroconversion. It is therefore important to identify indicators of a beneficial response: these include active liver disease and a short duration of infection. Better knowledge of the mechanisms of viral replication (involvement of a reverse transcriptase) and of the nature of the defects in the host defence that allowed the development of the chronic carrier state, will facilitate more rapid development in this field. Certain similarities between hepatitis B virus and HIV in the strategy of replication and the natural history of the viruses may give useful insight into the therapy of this infection.

Alpha-interferons also have some activity against hepatitis delta virus and non-A, non-B hepatitis virus but adequate clinical results are not yet available.

3.2.3 *Retrovirus infections*

The current epidemic of the acquired immunodeficiency syndrome (AIDS) has greatly increased research efforts on antiviral agents. With several million individuals already infected throughout the world, the best hope for these individuals at present is an effective treatment regimen. The most promising antivirals used so far against HIV were all developed for other purposes. Compounds previously known to have an inhibitory effect on reverse transcriptase were evaluated for activity against HIV in cell culture screening programmes. Unfortunately there is no standard screening test and great care must be exercised in evaluating the results. Different cells metabolize these compounds differently, and ideally a variety of test systems should be used.

The first anti-HIV agent to be identified was suramin. It was developed in 1916 as an antiparasitic drug. In 1979 it was shown to have an inhibitory effect on reverse transcriptase but it had not previously been tested against a virus disease. It was tested clinically in AIDS patients and was shown to have a virostatic effect. Nearly 100 patients with AIDS or AIDS-related complex were treated for one year; 30% of the patients became virus-free during treatment but viraemia was re-established after treatment was stopped. Because of the lack of clinical efficacy and the considerable toxicity observed, further studies with the drug were abandoned.

HPA-23 (ammonium-21-tungsto-2-antimoniate), which has activity against some animal RNA viruses, was shown to be a competitive inhibitor of HIV reverse transcriptase. However, the clinical toxicity observed, notably a reduction in platelets, and the absence of a significant clinical effect, discouraged further consideration.

Foscarnet sodium, previously mentioned for its activity against herpes viruses, is also a potent inhibitor of reverse transcriptase. Studies *in vitro* and *in vivo* have demonstrated (a) some activity against HIV and (b) its ability to cross the blood-brain barrier; the latter characteristic is important for all antivirals directed against AIDS because the brain is a site of viral replication. Clinical trials of this compound are in progress.

Zidovudine was originally developed as an anti-cancer drug and was later found to inhibit retrovirus replication. A double-blind, placebo-controlled clinical study of the effects of oral administration was initiated and then terminated when a monitoring committee observed a beneficial effect in the treated group. Patients receiving zidovudine showed increased numbers of circulating helper T cells, increased immunological capacity such as skin-test reactivity, a virostatic effect, weight gain, and improved general well-being. The drug was found to pass the blood-brain barrier. Toxic side-effects include severe anaemia and leukopenia, which may necessitate cessation of treatment and/or blood transfusions. Although the data are sufficiently positive to warrant use of the drug in AIDS patients, more effective and less toxic drugs are needed. Another problem with zidovudine in addition to its toxicity is the difficulty of obtaining an adequate supply of thymidine which is required to synthesize the drug. Significant amounts of zidovudine are necessary to treat patients (1 kg per 8 patients per annum) resulting in annual costs of several thousands of dollars per patient. Nevertheless, expanded and follow-up clinical studies are in progress.

Interferon has also been tested against HIV because of its broad-spectrum antiviral properties. *In vitro* studies were very encouraging, but so far no clinical benefits have been seen in AIDS patients. It may prove of value in combination with other drugs. Clinical studies have shown that alpha-IFN is effective against Kaposi's sarcoma in these patients.

A wide range of other agents, such as rifamycine (lipids composed of neutral glycerides) and ciclosporin, have been tried with no significant clinical benefit. A long list of immunomodulators including gamma interferon, interleukin-2, thymic humoral factors, ditiocarb sodium, etc., are currently being evaluated in clinical trials.

Among the more promising new antiviral compounds are 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine and 2',3'-dideoxythymidine. Clinical trials have already been started with dideoxycytidine.

The urgent need for additional antiviral compounds for the treatment of AIDS and other diseases has stimulated expansion of the search for new effective agents. In addition to screening of the existing compounds against HIV, the urgency of the problem as regards AIDS has resulted in the adoption of a truly targeted approach to the search. This is considerably helped by remarkable progress in the molecular biology of the virus and the identification

of several specific viral targets such as enzymes or regulatory proteins.

4. INFECTIONS FOR WHICH ANTIVIRAL DRUGS ARE NEEDED

Although considerable progress has been made in the past twenty years in the development of antiviral agents, we have barely made a start. Rotaviruses, respiratory viruses, herpesviruses, the hepatitis viruses, HIV, and the highly pathogenic arenaviruses and arboviruses all cause considerable mortality and morbidity and in all these cases there is a great need for effective antiviral agents. There is a particular need for antivirals for those viruses that have rapidly changing surface antigens, such as influenza, and for those with animal reservoirs since this complicates control measures. The development of antiviral drugs is most important also for diseases such as diabetes, arthritis, multiple sclerosis, cancer, and many other chronic and degenerative diseases, for which there is some indication that a viral etiological agent may be involved.

The ideal antiviral agent would be one, such as interferon, that has a broad spectrum of activity. However, it is likely that the least toxic compounds will be those that are very virus specific.

The greatest obstacle to effective antiviral therapy is viral latency. Following infection, the genome of some viruses, such as hepatitis B virus, herpesvirus, and HIV, becomes integrated in the normal cell and remains latent until some unknown stimulus induces viral replication. It is now possible to inhibit the replication of some viruses in the active stage but so far it has not been possible to affect the virus in its latent stage.

5. RECOMMENDATIONS

1. In order to develop antiviral agents in a rational manner, basic research should be encouraged to define the structure of target viruses, and to elucidate the mechanisms of virus replication and of virus-host interrelationships.

2. Antiviral agents should be used early in the infection to obtain maximum efficacy. Therefore, it is important that increased

efforts be made to develop simple and rapid techniques for viral diagnosis.

3. In order to make a statistically valid demonstration of efficacy as quickly as possible with a minimum number of patients, clinical studies should be performed in a double-blind, controlled manner, on well-characterized virus infections, with objective determinations of virological and clinical response.

4. Research on the development of delivery systems for controlled release and for targeting the agent to the affected cells must be encouraged; for example both monoclonal antibodies and retrograde axonal flow of agents attached to appropriate proteins should be investigated.

5. The emergence of drug-resistant virus mutants should be closely surveyed and monitored. For the treatment of infections involving such virus mutants it would be necessary to develop compounds with different modes of action, and different compounds in combination.

6. There are biological differences among interferon types and subtypes, and one type of interferon can potentiate the action of other types. The clinical performance of different natural and recombinant interferons should be compared. Structurally modified interferons should also be investigated.

7. It has been demonstrated that the effects of drugs used in combination may be synergistic. Further investigation of different combinations of several antiviral drugs, including interferons, should be encouraged. The possible advantages of such combinations include greater efficacy, lower toxicity, and smaller chance of the emergence of drug-resistant viruses. The effects of some combinations, however, may be antagonistic.

8. The development of antiviral and immunomodulatory agents for the treatment of chronic, recurrent, and latent infections should be encouraged. This would be facilitated by investigating why host defence mechanisms fail in the course of such infections.

9. Various *in vitro* screening and animal testing systems for the evaluation of antiviral agents against HIV should be compared, with the aim of developing standard procedures for the prediction of activity in man.

10. National authorities should be encouraged to expedite rigorous clinical evaluation of promising antiviral compounds for the treatment of AIDS patients, while exercising responsibility for ensuring the clinical safety of the compounds.

11. The scientific community and funding agencies should be encouraged to support and conduct further research on the development of antiviral agents and antiviral therapy for all pathogenic viruses, and, particularly, those that are of special importance in developing countries, whether or not they would be commercially profitable.

12. WHO should take an active part in the dissemination of information on the use of antivirals of proven efficacy such as amantadine and rimantadine for influenza A, aciclovir and vidarabine for varicella, zoster, and herpes simplex virus infections, ribavirin for infections caused by respiratory syncytial virus and some arenaviruses, and trifluridine, aciclovir, vidarabine and idoxuridine, alone or in combination with interferon, for some herpesvirus infections of the eye.

13. The use of agents that have not been shown to be clinically efficacious in sound clinical studies should not be encouraged. The use of such compounds, even if non-toxic, does considerable harm by misleading physicians and the public.

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