Current therapies using drugs to prevent infection, increase T-4 cell count

by Sean Hosein

ANTI-HIV AGENTS

DDC

Like AZT, the drug DDC (didexoycytidine) works by blocking the formation of the viral enzyme RT (reverse transcriptase), which stops the production of new viruses. Unlike AZT, DDC remains in the body much longer and can accumulate. This means that people using the drug will not have to take it as often as say AZT. But the level of DDC can rise to toxic levels, damaging peripheral nerve cells—usually in the hands and feet. Early trials of DDC were halted because of this problem. Newer trials of DDC have been taking place for over a year now in the United States, their results look promising. *New England Journal of Medicine* 1989;321(11):726-738.

One trial in California has used 21 people with AIDS or ARC. The subjects all had less than 400 T4-cells when they entered the trial. They were given either DDC 0.03 mg/kg of body weight per day or DDC 0.01 mg/kg of body weight three times per day (i.e. every 8 hrs) for 6 months.

Mild peripheral nerve damage was experienced by 3 patients in the 0.03 mg/kg group between weeks 8 and 17. No cases of nerve damage occurred in the other group. Nine out of nine patients receiving the 0.03 mg/kg/day dose showed a 50% reduction in levels of HIV p24-antigen. This is significant as p24 is usually produced whenever the virus is replicating. Of the nine people, four had a greater than 70% reduction in p24 levels. Only two of eight patients who received the 0.01 mg dose showed a 50% decline in p24 levels. Most patients had stable or transient increases in their T4 counts. No significant bone marrow toxicity was seen in either dose group, nor were appreciable changes in their immune systems noted. *V International Conference AIDS*, Montreal, 1989.

Alternating DDC + AZT

One way to deal with the toxicity of DDC is to use it for only short periods of time. But whenever people stop taking anti-HIV agents, viral replication increases rapidly. In order to avoid this researchers are conducting a trial of alternating DDC with AZT. Taking place at the National Cancer Institute, the trial has been under way for over 1.5 years. Eighteen patients were enroled who had either AIDS or advanced ARC (average of 118 T4-cells at the beginning of the trial). Subjects were given AZT 200mg/-4hrs for 7 days alternating with DDC 0.03 mg/kg/4 hrs (10 patients) or every 8hrs (8 patients) for 7 days.

Only 9 out of 18 patients have been on the original protocol without developing severe toxicity. Currently 16 patients are alive. Of the patients taking DDC every 4 hrs, there has been a sustained increase in the average T4 count amounting to 40 cells for over one year. There were also dramatic reductions in the level of HIV p24 in both groups. Patients reported increased energy and by the 6th. month had gained an average of almost 4 kilograms. *V Intl. Conf. AIDS*, Montreal, 1989. WBP 327. DDC is made by Hoffmann-La Roche, Nutley, New Jersey.

Understanding TNF

The major event leading to the development of AIDS is thought to be the reduced number and suppression of T4-cells (also known as CD4-cells). But T4-cells are not the only target of HIV. Another important cell of the immune system is the macrophage. These cells are not immediately killed when infected by the virus. Once inside the macrophage, HIV is safe from antibodies and even some anti-viral drugs and it is able to replicate. The macrophage then becomes a moving HIV factory, spewing out HIV where ever it goes. Infected macrophages are one means by which the virus is thought to enter and disrupt the brain. The HIV infected macrophage is not able to carry out its functions properly, resulting in a defective immune response. Macrophages play an important role keeping infections under control in the lungs and brain so it is not surprising that these sites are often locations of major life threatening infections in AIDS.

As a response to infection, macrophages often secrete chemicals to help organize and alert the immune system, one such chemical is TNF (tumour necrosis factor). TNF appears to cause a variety of effects including inflammation, fever and is associated with wasting syndrome. One of the events triggered by HIV infection is the production of TNF. In fact recent reports suggest that HIV infected people have higher than normal levels of TNF. Although this may explain some of the fevers and wasting seen in AIDS, the role of TNF in the context of HIV infection has not been clearly defined. Elevated TNF levels could also be as a result of the opportunistic infections seen in these people. *Journal of Virology* 1989;63(10):4404-4408 and *Journal of Clinical Investigation* 1989;84:733-737.

Whatever the cause, research indicates that in HIV+ people, the TNF system is out of control and that it actually contributes to immune suppression in general. See the sections below on "Taming TNF" and "Anti-Cancer agents" for related TNF matters. Some studies suggest that TNF may help against Kaposi's sarcoma while others show that it enhances HIV infection. It is possible that with the correct drug therapy, physicians could moderate the TNF system resulting in beneficial effects for their HIV+ patients. One drug which may do that is hydrazine sulphate.

Hydrazine Sulphate enhances TNF's antiviral action

Researchers in at the University of Texas have found an investigational drug which may inhibit TNF's damaging effects on cells while at the same time enhancing its anti-viral potential in test tube studies. The drug hydrazine sulphate has been used in experiments on people with cancer for over a decade in the USA and USSR. When used in test tube studies conducted at SUNY (New York) and Texas, hydrazine sulphate was able to increase the anti-viral effect of interferon-beta several hundred times. Although the virus used in these experiments was not HIV, TNF is thought to exert its anti-viral properties by causing the production of interferon-beta, a substance which does have anti-HIV activity. By itself hydrazine sulphate had no anti-viral activity. But the researchers suggest that the drug may be of use in treating viral diseases. In cancer trials the drug was shown to be of use in reversing the wasting syndrome seen in "terminal" cases. This property may also be useful in people with advanced HIV infection (see the section below on cancer for information on side effects and dosage). The drug is made in the USA by the Sigma company, St. Louis, MO. *International Journal of Immunopharmacology* 1989; 11(5):-501-507.

INFECTION FIGHTERS

Clinical trial of Interferon-gamma

People with severe HIV infection often have reduced number of T4-cells and accessory chemicals (such as interferons), relatively excess suppressor cells (T8-cells) and an immune system that is unable to deal properly with invading micro-organisms. Scientists have been conducting test tube studies at the Harvard Medical School with the cells taken from people with advanced HIV infection. When these cells are treated with interferon-gamma, increases in the T4-cell count are seen. The treated white blood cells also became activated and were able to mount an enhanced response against such disease causing organisms as HSV (herpes simplex virus), CMV and the fungus candida. *Infection and Immunity* 1989;57:3619-3628.

Researchers at UCLA have begun to publish the results of a clinical trial using the immune boosting/anti-viral chemical interferon-gamma. Twelve subjects were enroled in the phase I study which lasted for 8 weeks. All subjects had AIDS related Kaposi's sarcoma (KS) and were given weekly doses of interferon-gamma [each mg of IFN-gamma was equivalent to 20 million units of interferon activity] at one of three doses: 1, 0.1 or 0.01 mg/s.m. of skin surface (equivalent to 20 million, 2 million or 200,000 units/square metre). The drug was given either three times/week intravenously or 5 times/week intramuscularly. Before therapy the subjects had an average level of 56 T4-cells (normal values in non-HIV infected people are between 350-1334 cells), a T4/T8 ratio of 0.11 (normal value 0.84-3.05) and abnormally high levels of antibodies.

Due to the short period of time the subjects were given interferon, it is not surprising that there were no significant changes in T4-cell counts and other white blood cell levels. Nor were there any changes in the size of tumours. The most significant change (from a treatment perspective), however, was in the level of HIV p24. This viral protein appears to be a good indicator of HIV replication, as p24 increases usually reflect rising viral production. All subjects had decreases in their levels of p24 following treatment. IFN-gamma administration also resulted in the activation of more macrophages which could, over long term treatment, lead to an improved immune system (it is possible that the decrease in p24 was due to an enhanced immune response caused by interferon). The IFN-gamma used in this study was made by Genentech Inc., San Francisco, California. *Cellular Immunology* 1989;123:316-324.

Interferon + Interleukin

Current anti-HIV strategies using drugs such as AZT and DDC are aimed primarily at preventing new infection. These drugs do virtually nothing for chronically infected cells which act as reservoirs for HIV. This must be taken into account when designing treatment strategies for HIV+ people. A group of substances which may help the body suppress such reservoirs are the cytokines. These are chemicals such as the interferons and interleukins all of which are produced by the body. Reduced levels of cytokines are thought to be one of the reasons why the immune systems of HIV+ people cannot defend the body properly against invading organisms. Cytokines have been used as potential anti-cancer and anti-viral agents with some success. For instance interferon-alpha has been of use in some cases of kaposi's sarcoma and one trial of interferon-beta showed it to be effective in treating CMV (cytomegalovirus) infections.

Scientists at the Duke University Medical Centre, Durham, North Carolina, have conducted test tube experiments with various cytokines and found that the combination of the drugs interleukin-2 with interferon-gamma produced may be a good candidate for human studies. In their experiments the two drugs together were able to activate white blood cells and cause them to attack and destroy HIV infected cells. By using interferon-gamma simultaneously with IL-2, scientists were able to reduce the toxicity of IL-2 while providing an improved immune response. A pilot study of IL-2 with AZT is under way in the USA. *Journal of Biological Response Modifers* 1989;8:501-510.

Taming TNF

Infection by HIV is thought to begin a series of events which eventually leads to AIDS. The virus is known to attack the very defenders of the immune system, the T4 cells. Long term infection leads to a progressive decline in the number of T4 cells and a relative increase in the amount of T8 or suppressor cells. HIV infected cells also produce substances which further reduce the competence of the immune system. Another means by which damage occurs is that the body then begins to attack itself especially elements of the immune and nervous systems. Due to the interplay between so many factors, it does not seem that advanced HIV disease can be defeated using drugs which are just anti-HIV agents.

One of the complex system thrown out of balance by HIV infection is the TNF system (see the section "understanding TNF" earlier in this issue). TNF levels seem to be elevated in HIV+ people. Research suggests that TNF—in combination with HIV—may cause the body to produce a substance which inhibits the activity of interferon, a natural anti-viral/cancer chemical. Indeed a recent study has found that as HIV infection worsens levels of the interferon inhibitor rise (the researchers found that people with severe HIV infection [AIDS, AIDS-related Kaposi's sarcoma and AIDS-related lymphoma] all had high levels). People with no symptoms of HIV infection along with people classified as ARC had no detectable levels of this inhibitor but they all had high levels of normal interferon.

Interferon inhibitors have also been found in patients with other diseases in which immune suppression plays a role. The scientists think that the production of the inhibitor is a means by which retroviruses, such as HIV, can overcome the body's defences. Retroviral infection also tends to cause production of an substance called PGE (prostaglandin E2). PGE2 has been shown to interfere with immunity and interferon production. Researchers have found that drugs which protect cells from PGE2 can raise interferon production in test tube studies.

Thus, if clinicians could find ways of controlling the various immune suppressive effects of HIV disease, the results could benefit their patients. One drug which may afford this possibility is indocid (generic name:indomethacin). The prescription drug has been used for many years (in Canada and the USA) in patients with arthritis so doctors are familiar with its use. Clinical trials of this drug in HIV people are planned. Another drug which may help reduce immune suppression is hydrazine sulphate which rescues cells from the toxic effects of TNF. This drug has been used in cancer trials in the USA with virtually no severe side effects. Another drug which may be useful is naltrexone, which should be accessible through Canada's Emergency Drug Release Programme (EDRP). In a recent 4 year trial of naltrexone (in people with AIDS) in the US, the drug appeared to prolong survival possibly by reducing levels of the interferon inhibitor (*Intl. Conf. AIDS*, Montreal, 1989. Poster MC 62). See Treatment Update #7 for details of naltrexone. References: *American Journal of Medicine* 1989;87:405-407, *J. of Clin. Invest.* 1989;84:738-743.