HAEMOFACT HIV TREATMENT NEWS

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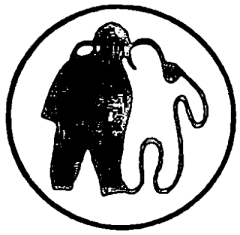

HIV TREATMENT NEWS

For people with haemophilia and HIV

HIV TREATMENT NEWS is a new occasional publication made available to members of the Haemophilia Society. It will be issued at least twice a year and more often if important medical matters have to be brought to attention of people with haemophilia and HIV.

The Society is indebted to Dr Mike O'Doherty and Sister Chris Harrington for their technical assistance with this new publication which we hope you will find useful.

PLEASE LET US KNOW WHAT YOU THINK both about, HIV TREATMENT NEWS as an idea and future issues you would like to see discussed in its columns: it is YOUR fact sheet and we want you, the reader, to feel that you have a real part to play in its production.

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ddI

THE Medical Research Council in collaboration with its French partners, INSERM, have recently launched the ALPHA trial, a trial of diodeoxyinosine (ddI) in patients with progressive HIV disease who are unable to take zidovudine because of side effects. In this article, the facts about ddI are explained and the need for a trial is outlined.

What is ddI?

ddI (diodeoxyinosine, didanosine) is a new antiviral drug which is active against HIV in laboratory tests. The structure of ddI is similar to zidovudine (AZT, Retrovir). Experiments in virus infected cell cultures suggest that it works by inhibiting HIV-reverse-transciptase, (an essential metabolic reaction in virus infected cells) in a slightly different manner to AZT. ddI is taken orally twice a day and comes as a sachet containing a powder which is dissolved in water and needs to be taken on an empty stomach. ddI is broken down by acid and therefore the sachet contains a buffer to neutralise the stomach acid. This means that all the sachet must be taken at the same time. Chewable tablets may be available next year.

Is ddI toxic?

Most drugs have side effects, ddI is no exception. Early studies showed that ddI sometimes gave people numbness and pain in the feet (peripheral neuropathy). Fortunately, these symptoms improve if the drug is stopped. It is likely that this occurs much less often if low doses of ddI are used as in the current trial. Recent experience from the USA suggests that a few patients (about 1 per cent) get acute pancreatitis (inflammation of the pancreas) which may present with sudden severe stomach pains. This can be very severe and a few people have died from it. People who have had pancreatitis in the past should not take ddI.

Does ddI work in patients with HIV disease?

Early work on ddI in small uncontrolled studies suggests that ddI decreases the level of viral proteins (p24 antigen) and increases the level of CD4 counts (helper T lymphocytes) circulating in the blood. These preliminary results suggest that ddI may act in a similar way to zidovudine. However, we do not know yet whether ddI actually helps patients feel better for longer and live longer.

Clinical trials on ddI

Before patients can be confident that ddI is a safe and effective drug to be used for HIV disease, proper clinical trials are required. In the USA, a number of trials have recently been started but they will not answer all the questions about ddI, particularly as many more patients are receiving the drug in an uncontrolled fashion in the so-called "parallel track". However, the US experience is sufficiently large (about 10,000 people have already taken ddI) to give us good information on the drug's side effects.

The MRC/INSERM ALPHA trial

The MRC in collaboration with INSERM has launched a clinical trial of ddI. It is expected that Holland, Australia, Switzerland and the Nordic Countries will also participate in the trial. The main aim of the trial is to determine whether ddI is effective in prolonging life and preventing the progression of HIV disease to AIDS. Also, the trial will compare two doses of ddI in terms of both efficacy and toxicity.

At present there is no evidence that ddI is as effective as zidovudine so it was considered unethical to offer ddI to patients who can still take zidovudine. However, patients who cannot take zidovudine will be eligible for the ddI trial. ALPHA is a randomised double blind trial. It is randomised so that patients in the different treatment schedules will be as similar as possible in the characteristics which may affect their response to the drug. Double blind means that neither the patient nor his clinician knows which treatment schedule he is taking; this is very important as it ensures that the trial is a fair test of the different treatments as neither patient's nor doctor's decisions can be influenced by knowing what treatment they are on. Obviously the statistician at the Trial Centre knows the code and the trial is constantly monitored by an independent Data and Safety Monitoring Committee which sees all the results and will decide whether to recommend early publication of the results of the trial so that all patients can benefit from the best treatment.

The trial has a rather novel, although completely scientific design. Patients, in discussion with their clinician, will be offered two alternative options in the trial.

Option A is a randomisation between high dose ddI, low dose ddI and placebo (dummy sachets) this is because we do not yet know how effective and how toxic ddI is. Patients who are uncertain whether they wish to take ddI or not will want to choose Option A. Results obtained from patients entering this option will give rapid and clearcut results on whether ddI is effective in HIV disease. At any stage after randomisation, if patients or their clinicians feel that they are deteriorating, in spite of taking the trial sachets, the patient can be switched to ddI (Option B), in case they were on the inactive preparation.

Option B is a randomisation between high dose ddI and low dose ddI but not the placebo. Patients who are certain, in spite of the lack of knowledge about the efficacy of ddI and the known risk of toxicity, that they want to take ddI will want to choose Option B. Option B will give information on the relative toxicity of the two doses of ddI but may not tell us how effective it is.

It is hoped that this novel approach to HIV clinical trial design will enable good trials to be conducted which can combine the advantages of a placebo controlled trial which provide rapid, clearcut, reliable answers and also the flexibility to enable patients to take a new drug whenever they and their clinician think it is appropriate.

ddI — the future

Many HIV workers now believe that the best chance of a major improvement in the treatment of HIV is to develop combination treatments. This approach has worked both in the treatment of tuberculosis and some cancers. If ddI is shown by the present trials to be safe and effective then ddI and zidovudine may then be one of the first combinations to be tested.

AZT (Zidovudine); Past, Present and Future

C.R.M. Hay, The Royal Liverpool Hospital

AZT (Zidovudine, Wellcome) has been used increasingly over the past three years for the treatment of HIV infection, and remains the only antiviral drug in common use for this condition. First synthesised as far back as 1964, AZT has been known to be active against retroviruses for at least 15 years (HIV was first recognised as a retrovirus in 1984).

Retroviruses reproduce within cells by making copies of their genetic material, nucleic acid, from the host-cell's animo-acids using reverse-transcriptase, an enzyme peculiar to this type of virus. AZT is structurally similar to one of the building-blocks for the nucleic acid which forms the genetic material of both human cells and viruses. AZT substitutes for thymidine in the growing nucleic acid chain of the virus during viral replication, inhibiting the enzyme reverse-transciptase, and reducing the number of copies of the virus made. There are now a range of other drugs structurally similar to other vital DNA/RNA building-blocks which work in a similar way to AZT and which are being tested as anti-viral agents in HIV infection. These are known collectively as reverse-transciptase inhibitors.

Efficacy:

AZT has been shown to inhibit HIV-virus replication, and to reduce the number of viruses circulating in infected individuals. This is often associated with weight gain and an improvement in general wellbeing, and may be accompanied by stablisation or sometimes even a temporary increase in the T4 helper cell count. AZT has been shown to defer the onset of AIDS or AIDS-related complex, and to improve both the outlook and the quality of life of those patients who already have AIDS or AIDS-related complex. It is not a cure, but is nevertheless an important therapeutic advance.

Side-Effects:

AZT causes nausea in a small proportion of patients but is generally well tolerated. Unfortunately, AZT acts not only on the virus, but interferes also with human metabolism. This has its principal effect on the bone marrow, resulting in abnormal production of blood cells. Most patients on AZT will develop macrocytosis (large red cells) and many will develop mild anaemia, however these do not usually cause a significant problem for the individual. 5 per cent of patients without symptoms from their HIV infection become more severely anaemic on AZT and require regular blood transfusion. This problem is much commoner in patients with AIDS, 50 per cent of whom may require transfusion. This is not generally considered a reason for stopping the drug. A proportion of patients also suffer reductions in platelet and white cell counts, particularly those with AIDS or AIDS-related complex who often have low platelet and white cell counts to start with. If these changes are severe, AZT is either stopped or given intermittently. The effects of AZT on the bone marrow are generally temporary and disappear when the drug is withdrawn. In susceptible individuals these effects usually happen within the first three months of treatment and so it is usual to check the blood count at least monthly for the first three months of treatment and slightly less frequently thereafter.

Who should be treated with AZT?

There seems little doubt that patients symptomatic from their HIV infection, those with AIDS or AIDS-related complex, do benefit from AZT. Most clinicians would also start AZT in asymptomatic patients with T4 helper cell counts of 0.2-0.3 x 10/9/1 on the basis that, without treatment, these patients have an increased risk of developing problems within two or three years. Whether AZT should be given to all HIV antibody positive patients is far more contentious. Although a recent American study showed a reduced incidence of progression to HIV related symptoms in well patients, treated with AZT over a two year period, longer follow-up is necessary before AZT can be recommended for all HIV seropositive patients. Resistance to AZT is very common after one or two years of treatment and it may be better to reserve AZT for symptomatic patients and those with low T4 helper cell counts.

Resistance:

Several studies have now shown that partial resistance to AZT resulting from mutation of the virus is extremely common after 12 to 24 months of treatment. Complete resistance to AZT has been noted in some patients with AIDS. Some benefit continues to be noted even in patients with partial resistance, however, and so it is usual to continue AZT for as long as it is well tolerated. The techniques used to detect resistance are research tools and not suitable for routine use. Current reserach to overcome both resistance and the potential side effects include clinical trials of other reverse-transcriptase inhibitors used in sequence with AZT, (one month's AZT then one month of the other drug, then repeat the cycle). If practice bears out the theory, this combination will reduce the problem of resistance and avoid the side effects of both drugs.

The Future:

Although AZT remains the mainstay of antiviral treatment for HIV infection, it will soon be joined by other more powerful reverse-transciptase inhibitors, probaby used sequentially to minimise their side effects. Other drugs including modified sugars offer the promise of less toxicity and the potential for cure, but are still in the development stage, and have not been fully evaluated.

Aerosolized Pentamidine and the prevention of Pneumocystis Carinii Pneumonia (PCP)

The need for prevention

Pneumocystis Carinii Pneumonia (PCP) is the most common infection in people with AIDS — as many as 85 per cent may develop PCP at some stage. It is possible to have PCP more than once, so inevitably, attention has turned to preventing recurrence. If you have had PCP in the past, then preventative treatment (prophylaxis) significantly lowers the risk of another episode occuring.

For those who have signs of immune deficiency, indicated by a T4 lymphocyte count of less than 200 cells/mcl, there may be up to a 60 per cent risk of developing PCP 18 months on. So far, studies show that this risk can be substantially reduced with prophylaxis.

The Treatment

The treatments which have been found to be effective include Septrin, Dapsone and Fansidar which are taken by mouth. Some people are unable to tolerate these and develop side effects such as skin rashes and nausea.

The alternative treatment is a drug called Pentamidine given by inhalation of an aerosol from a nebuliser. A solution of Pentamidine is placed within a nebuliser and air or oxygen is passed through it. A mist is formed which is then breathed into the lungs. (This way of giving treatment has been used for some years by people with asthma). The size of the particles (droplets) in the mist is of importance to the effectiveness and the potential side effects of the Pentamidine. Different types of nebuliser produce different particle sizes and further studies are being undertaken to evaluate how best to get Pentamidine to the lungs.

The doseage of Pentamidine

A variety of doses have been tried using different nebulisers. For example, on current evidence, 150mg (6ml solution) is effective given through a System 22 Mizer nebuliser. If this has side effects which are difficult to tolerate, an alternative nebuliser, a Respirgard II, can be used. A Pentamidine dose of 300mg (6ml solution) is used with this system.

An air flow rate through the nebuliser of 6-8 litres a minute is needed. In hospital this may be achieved through a piped air/oxygen system or cylinder. A suitable portable electrical compressor may be used at home.

How often?

Currently it appears that once a month treatment with nebulised Pentamidine will provide adequate protection. It takes about 30 minutes to inhale the Pentamidine.

Potential side effects of Pentamidine

When Pentamidine is being inhaled, local side effects are possible. These may include:

Coughing — Coughing and a feeling of tightness in the chest can be a result of constriction of the bronchi, the series of branching tubes in the lungs into which the trachea (windpipe) divides. If these symptoms occur, a solution containing a drug (Ventolin) which dilates the bronchi, may be given through the nebuliser before the Pentamidine treatment.

It takes about 10 minutes to inhale the Ventolin.

Metallic taste — Rinsing mouth with fruit juice at intervals and/or sucking a boiled sweet immediately after treatment may help.

Sore throat — Taking sips of water every few minutes during and after treatment may relieve this.

Fatigue/dizziness — breathe normally, slowly and evenly. Take some breaks during treatment (stop the air flow during breaks).

Some people also experience nausea and/or increased saliva production.

As knowledge of how to deliver Pentamidine effectively is growing, these side effects are lessening.

Home Treatment

Hospital supervision is required at first to assess the effect of the treatment and whether pre-treatment with Ventolin is necessary. People may then be taught to treat themselves at home — those used to managing their haemophilia home treatment pick this up very quickly.

To protect those around you at home, treat yourself in a well-ventilated room and turn off the air flow to the nebuliser if you need to take a break. Pentamidine is a skin irritant so contact with eyes or skin should be avoided.

A comfortable upright chair and some good music are recommended.

PCP prophylaxis is making an important contribution to the health of many people with haemophilia and HIV infection. Your individual needs and updated information should be discussed with your Centre staff.

Chris Harrington, Clinical Nurse Specialist, St Thomas' Haemophilia Centre

HIV and your Haemophilia Centre

What should you be able to expect?

Follow-up appointments — should be available every three to six months. These will need to be more frequent for those who have symptoms and/or require treatment.

Should include: physical examination by doctor, your health history since last seen, blood tests including T cell subsets, explanation of any test results

Time for discussion —
of available treatments and their relevance for you
— to update your knowledge of any new developments

HIV antibody testing — for those sexual partners who have, following discussion, chosen to have the test, and further appointments for results to be considered

Referral to appropriate specialists — eg ophthalmologist, dermatologist, dentist

Counselling available — for you and anyone close to you, eg partner, family members

PARTNERS AND FAMILY MEMBERS SHOULD BE ACTIVELY WELCOMED AT THE CENTRE

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