Randomised placebo controlled trials in HIV infection: to be or not to be?

With advances in the treatment of human immunodeficiency virus (HIV) infection, we are faced with the dilemma of how best to treat patients at all stages, from asymptomatic to serious disease. Treatments have become part of accepted clinical practice without information from properly designed trials. In other diseases, the initiation of scientifically based studies appears to be straightforward. In HIV infection, however, there are a myriad problems. These are illustrated by the controversy surrounding multicentre placebo controlled trials to assess whether the early use of zidovudine will delay progression to symptomatic disease and ultimately prolong life.

Zidovudine was shown to be beneficial in a multicentre randomised placebo controlled trial started in February 1986 in 282 patients with *Pneumocystis carinii* pneumonia or AIDS related complex.¹ Mortality was significantly lower in the treated patients (1/145) than in those receiving placebo (19/137). Furthermore, the 24 week probability of developing opportunistic infections was reduced. As a result, zidovudine was released in Europe in the spring of 1987 and used for patients with symptomatic HIV disease in all subgroups of group IV of the Centers for Disease Control (CDC) classification of HIV infection. This extension of its use for patients other than those enrolled in the controlled trial was compassionate and logical, considering the prognosis of patients with symptomatic disease and the mode of action of the drug. Doctors currently assume that all patients with symptomatic disease will benefit from treatment. The side effects of treatment include nausea, myalgias, insomnia, headache, and myopathy. In addition there is a single report, not yet confirmed, of encephalopathy associated with stopping or reducing the dose of zidovudine. The most important toxicity occurs in the bone marrow, and causes megaloblastic macrocytic anaemia, leukopenia, neutropenia, and red cell aplasia.²⁻⁶ Reports have suggested that the duration of the effect of zidovudine is limited and that viral strains with reduced sensitivity may emerge in a proportion of patients treated for longer than six months.⁷⁻⁹ With this increasing experience in treating symptomatic HIV disease, the next question to ask is whether there is a role for the drug in treating people with asymptomatic HIV infection.

A review of epidemiological data suggests that the

major risk factor for progression to AIDS is time, or duration of infection. Data from cohort studies vary, but it appears that 50-75% of infected people may progress to symptomatic disease in 10 years.¹⁰⁻¹⁴ From these studies various laboratory markers have been identified as being associated with a more rapid progression to symptomatic disease. These include anaemia, lymphopenia, neutropenia, raised erythrocyte sedimentation rate, decreased T-helper cell count, raised serum B2 microglobulin concentration, the appearance of serum p24 antigen, the loss of the respective antibody, and an increasing IgA concentration (Schechter MT, *et al.* International conference on AIDS, Stockholm 1988). No one marker is particularly useful in an individual patient, but a cocktail of markers, such as low CD4 count, raised B2 microglobulin concentration, decreased packed cell volume, and p24 antigenaemia, has been shown to be predictive, with a three year progression risk of 7% in patients lacking these markers, 17% in patients with one abnormality, and 57% in patients with two or more abnormalities.¹⁵

These data give rise to speculation that giving early antiviral treatment would decrease progression to symptomatic HIV disease by limiting viral replication. A logical approach to studying a drug with considerable toxicity would be to begin trials in patients with a profile of laboratory markers associated with more rapid progression to symptomatic disease. Such trials have already begun, but it may take several years to obtain an answer, and that would apply to only a minority of people with antibody to HIV. Showing efficacy in that subgroup would make it more difficult to start placebo controlled trials in other patients with antibody to HIV, and patients and doctors might assume, perhaps wrongly, that zidovudine would benefit all patients.

An alternative approach would be to randomise to treatment or placebo all patients with antibody to HIV and to stratify for markers in such a way that there is equal distribution between the two arms of the trial. The Medical Research Council (MRC) in the United Kingdom and the Institut Nationale de la Santé et de la Recherche Médicale (INSERM) in France have begun a trial with this design.

At the moment we do not know whether patients who are asymptomatic would benefit or be harmed by

an antiviral drug, or whether treatment should be delayed until the symptomatic phase of infection. This question provides the ethical support for a placebo controlled trial of zidovudine, as there is no standard treatment for patients with asymptomatic HIV infection. Lay and medical communities are, however, raising objections to placebo controlled trials. Calls have been made for trials using historical controls, or trials in which the patient or doctor decides who will receive the drug. There have also been criticisms that placebo controlled trials have been designed without acknowledging the patients' best interests or the stresses of HIV infection.¹⁶

The problem associated with abandoning placebo controlled trials would be that the scientific and statistical validity of a trial depends on a proper design. Without a randomised placebo controlled trial, one cannot guarantee that the two groups of patients will be the same; that the groups will get the same management without bias; that the symptoms, signs, and end points of both groups will be recorded in the same way; and that the effect seen is due to the drug. Assumptions might be made that zidovudine was or was not beneficial, either of which might be incorrect, and such an error would be unacceptable.^{17,18} Sufficient evidence is required to convince patients to take the drug, doctors to prescribe it, agencies to licence it, and governments to pay the bill.

The hepatitis B virus (HBV) was identified in 1970.¹⁹ In the late 1970s interferon was shown to have an antiviral effect on HBV.²⁰ After 12 years of small uncontrolled trials or controlled studies of small numbers of patients there is not yet sufficient information to alter clinical practice; that is, to convince patients and doctors that interferon is an effective treatment of HBV carriers.^{21,22} A properly designed trial of patients with asymptomatic HIV infection must be undertaken before a drug that possibly does more harm than good is given indiscriminately.

A placebo controlled trial stresses both patients and doctors. It is difficult to explain the design of such a trial to the patients, and doctors may shy away from the long and detailed discussions required. This may cause problems with accrual to the study and may lead to differences in the information available to patients. Patients with antibody to HIV have numerous sources of stress and anxiety resulting from their infection and its physical, social, and psychological implications. For some patients, participating in a trial allows them to take a more active part in managing their infection and takes them away from the role of victim. Seeing a doctor at regular intervals gives them confidence that disease will be detected earlier. For other patients, however, the frequent visits and the stress of constantly taking capsules that may or may not be the drug will unbalance the mechanisms that they have acquired to cope with their infection. A common reason given for not joining a trial is that the tablets and visits are constant reminders of infection.

Another concern is the blinding of a trial. Although this is difficult, the doctor and patients in the MRC/

INSERM trial will be blinded to the results of the mean corpuscular volume, red blood cell count, packed cell volume, and p24 antigen concentrations. Other trials have reported drug sharing, which is a problem that can only be overcome by giving patients information that emphasises the philosophy of the trial. Random testing for the presence of the drug in patients receiving placebo and those receiving active treatment will detect the extent of drug sharing.

The deluge of information in the media influences patients' perceptions of current views about the treatment of HIV infection. Some articles suggest that all placebo controlled trials are wrong and all patients should receive drugs on request, including zidovudine. Other groups claim that all available drugs are too toxic and other approaches such as a "healthy lifestyle", a positive attitude to survival, taking vitamins, and a balanced diet are sufficient treatment. The data on progression to symptomatic disease and clinical trials using conventional treatment confront this philosophy. Most of the agents reported extensively in the media have been assessed only *in vitro* or in preliminary phase I trials. Examples exist in which a drug's *in vitro* efficacy has not predicted clinical efficacy. Phase I studies tell us about side effects and pharmacokinetics. They may provide clues to efficacy, but these clues can be misleading. These early uncontrolled studies, which are subject to selection bias and rash verdicts, often convince the media and therefore our patients. We all desire the discovery of the ideal agent; a drug with low toxicity and high specificity for HIV and HIV infected cells, which protects uninfected cells, penetrates the central nervous system (CNS), is orally absorbed, has a long half life, and is produced at low cost. Unfortunately an ideal agent does not yet exist, but media coverage feeds the hope for such a discovery. The frustration that it does not exist may turn into anger directed at the medical community. We must rely on the trust inherent in the relationship between doctor and patient and the provision of a balanced interpretation of all information available to counter the frustrations and anger of press and activist groups that threaten the scientific study of treatment.

The advent of large scale trials in asymptomatic people will interfere with the numerous studies of seropositive cohorts that are currently in progress. These include studies of specific immunological responses to HIV, virus variations, and neurological and neuropsychometric studies, to give but a few examples. In the coming months or years the placebo arms of the trials will probably become the natural history cohorts of tomorrow. A major problem is that clinical and basic scientists may want to break the code as to who is receiving the drug and who is taking placebo before the end of the trial, which would unblind the study.

A study of 15 patients with symptomatic disease who were treated with zidovudine for longer than six months has shown that viral isolates showed some decrease in sensitivity in a plaque reduction assay using a CD4 receptor bearing HeLa cell line.^{8,9} Isolates

from five patients showed 100-fold decreases in sensitivity. The remaining isolates from seven patients showed small decreases. In general, longer durations of treatment were associated with less sensitive virus. There are a number of caveats to consider. The study was small and the clinical implications not clear. Virus was recovered from only one third of the patients studied. In vitro sensitivity does not always correlate with in vivo sensitivity. The emergence of reduced sensitivity was not associated with poor clinical response or increased serum p24 antigen concentrations. Furthermore, the less sensitive isolates were still sensitive to other dideoxynucleosides and to phosphonoformate. Acyclovir resistant herpes simplex viruses tend to occur in immunocompromised patients and, interestingly, are usually less pathogenic in animals.²³ It would be wrong to assume that the phenomenon of reduced sensitivity to zidovudine observed in patients with symptomatic disease will emerge to the same degree in asymptomatic patients. Most importantly, zidovudine reduces mortality and morbidity in symptomatic disease and is the only antiviral currently licensed. These findings should not theoretically alter clinical practice or clinical trials, but the phenomenon should be studied rapidly in larger numbers and should include studies of sensitivity in patients receiving treatment, their sexual partners, patients in whom treatment is stopped to assess how long less sensitive strains persist without the selection pressure of treatment, patients receiving combinations of antivirals, and also patients in asymptomatic trials.²⁴ To this end, a proportion of patients in the MRC/INSERM trial will have the sensitivity of viral isolates monitored throughout the trial.

Treating HIV infection has involved doctors from a wide variety of specialties, with and without expertise in large multicentred clinical trials. Different centres require varying levels of support. Many centres are already overburdened with clinical care and understaffed. The network of trial centres set up in the UK and France with support from the MRC and INSERM will, it is hoped, provide a proper framework for assessing antiviral and other treatments in large numbers of patients and provide results that can improve clinical care quickly.

Despite the numerous issues surrounding such trials, it is important to define the role of zidovudine in asymptomatic people. Our treatment of asymptomatic patients infected with HIV depends on attempting to slow the progression of disease with a treatment that is acceptable to patients and doctors. If there is not an accepted treatment only large placebo controlled trials will give us the answers. We need to establish the role of zidovudine before it is prescribed indiscriminantly and potentially causes more harm than good.

Karen Gelmon,
Senior Lecturer
Ian V D Weller,
Reader

Academic Department of Genitourinary Medicine,
University College and Middlesex School of
Medicine, London W1N 8AA

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