indefinitely such as zidovudine. With a daily dose of 500 mg zidovudine a person receives 2×10^{20} molecules, or 2×10^6 for every human cell, every day for the rest of his life. By contrast, after 11 years of research the HIV hypothesis has yet to identify a single molecule that could be pathogenic.¹³ In view of this and the complete failure of the HIV hypothesis to produce public health benefits, non-HIV hypotheses must be studied more carefully.

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Response: Arguments contradict the "foreign protein-zidovudine" hypothesis

Caroline A Sabin, Andrew N Phillips, Christine A Lee

In 1991 Duesberg challenged researchers to provide either data on "controlled epidemiologic studies comparing matched hemophiliacs, with and without HIV, or epidemiological evidence that the mortality of hemophiliacs is increased by HIV."¹ We and Darby *et al* have provided that evidence.^{2,3} Duesberg's commentary⁴ requires further comment.

HIV may be enough to cause AIDS

It is incorrect to conclude that HIV is not sufficient to cause AIDS simply because some of the infected patients in our study had not developed AIDS by 10 years after seroconversion. Only longer term follow up studies will finally establish whether all HIV positive patients would, given enough time, ultimately develop AIDS. In the United States around 3800 haemophilic patients have reportedly developed AIDS out of 9000 who have been infected⁵ (World Federation of Hemophilia, personal communication, 1995), a far higher proportion than that quoted by Duesberg in arguments against the HIV hypothesis.

Duesberg's foreign protein-zidovudine hypothesis predicts that haemophilic patients will not develop non-immunodeficiency diseases such as dementia. Given the low prevalence of some of the 26 different AIDS defining conditions it would not be expected that we should witness all conditions among our 17 patients. However, dementia is well documented in HIV positive haemophilic patients and occurs with a similar prevalence to that in other exposure categories (Xen Santas, Centers for Disease Control, personal communication, 1995). Among all 111 HIV positive haemophilic patients at this hospital, dementia occurred in six.

Duesberg points out that lifetime usage of concentrate may be expected to be different between a 60 year old and a 14 year old (our pair 3). Unfortunately, lifetime usage of concentrate was not available in these patients and therefore usage patterns over 10 years were used. However, it is important to remember that clotting factor concentrate was introduced in our centre in 1978 on average, so that age differences in the pairs may suggest larger differences in lifetime usage than actually existed. Even when the analysis was restricted to pairs in whom the HIV positive patient was younger than or the same age as the HIV negative

patient (eight pairs) the results remained similar: four of eight HIV positive patients developed AIDS defining diseases compared with none of the eight HIV negative patients. Furthermore, since 1980 none of 400 HIV negative haemophilic patients registered at this hospital has developed AIDS despite having received clotting factor concentrates on average since 1978, and CD4 counts in these patients have been similar to those of HIV negative heterosexual subjects.⁶

Contrary to Duesberg's assertion, sexual transmission of AIDS has been observed at our centre. At the Royal Free Hospital sexual transmission of HIV to partners with no other risk factors for HIV has occurred in three cases. Of these infected partners, one developed AIDS and died (the haemophilic partner of this patient also died with AIDS), one was symptomatic with a CD4 count of zero but remained AIDS free, and the third remained asymptomatic but with a CD4 count of $0.2 \times 10^9/l$. No wives of any other haemophilic patients at our centre have developed AIDS.

Patients are given zidovudine because they are ill

It is not true that most British haemophilic patients infected with HIV have been given zidovudine since 1987. Initially patients were given zidovudine after the development of AIDS. Subsequently, since around 1989, patients have been given zidovudine once their CD4 count has fallen below $0.2 \times 10^9/l$ or after the development of symptomatic disease. Similar recommendations are made for pentamidine or co-trimoxazole as prophylaxis against *Pneumocystis carinii* pneumonia. Consequently, by the time patients begin zidovudine and pentamidine they have low CD4 cell counts and are usually symptomatic.

Observational studies often show that patients given zidovudine have a worse prognosis than untreated patients.⁷ Patients receiving zidovudine are selectively treated because they are ill. The interpretation of findings from these studies should not therefore be that zidovudine increases the risk of AIDS. Of the nine patients developing AIDS in our study, seven received zidovudine only after an initial AIDS diagnosis when immunological deterioration had already occurred. There is no possibility, therefore, that either

HIV Research Unit,
Department of Public
Health, Royal Free
Hospital School of
Medicine, London
NW3 2PF

Caroline A Sabin, lecturer in
epidemiology and medical
statistics

Andrew N Phillips, reader in
epidemiology and biostatistics

Haemophilia Centre and
Haemostasis Unit,
Department of
Haematology, Royal Free
Hospital and School of
Medicine, London
NW3 2PF

Christine A Lee, director
haemophilia centre

Correspondence to:
Dr Sabin.

zidovudine or pentamidine had a causal role in the initial development of symptomatic disease in these patients.

Finally, though there may be some beneficial effect of high purity clotting factor concentrates on the immune systems of patients with haemophilia,⁸ there is little evidence that this has translated into clinical benefit for these patients.⁷ Conversely, a recent paper has suggested that increased usage of intermediate purity clotting factor concentrates may be beneficial for HIV positive haemophilic patients.⁹

Despite the provision of new data which support the HIV hypothesis for the development of AIDS, the arguments proposed by Duesberg in his commentary remain unchanged and contradict the "foreign protein-zidovudine" hypothesis. For the benefit of patients infected with HIV it must now be time to move on to enable researchers to devote time to the real issues at hand.

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Magnitude of benefit from earlier thrombolytic treatment in acute myocardial infarction: new evidence from Grampian region early anistreplase trial (GREAT)

John Rawles

Abstract

Objective—To generalise from the results of the Grampian region early anistreplase trial (GREAT) and to express the benefit of earlier thrombolysis in terms of lives saved per hour of earlier treatment.

Design—Multivariate analysis of a randomised double blind trial.

Setting—29 rural practices in Grampian region and teaching hospitals in Aberdeen.

Subjects—311 patients with suspected acute myocardial infarction and without contraindications to thrombolysis who were seen by their general practitioners within four hours of the start of symptoms.

Interventions—Anistreplase 30 units given intravenously, either by general practitioners before hospitalisation or later in hospital.

Main outcome measure—Death within 30 months of entry into trial.

Results—Death within 30 months was positively related to age ($P < 0.0001$) and to delay between start of symptoms and thrombolytic treatment ($P = 0.0004$). However, the probability of dying rose exponentially with earlier presentation, so death within 30 months was negatively related to the logarithm of the time of randomisation ($P = 0.0163$). In patients presenting two hours after start of symptoms each hour's delay in receiving thrombolysis led to the loss of 21 lives per 1000 within 30 days (95% confidence interval 1 to 94 lives per 1000) ($P = 0.03$) and 69 lives per 1000 within 30 months (16 to 141 lives per 1000) ($P = 0.0004$).

Conclusions—The magnitude of the benefit from earlier thrombolysis is such that giving thrombolytic treatment to patients with acute myocardial infarction should be accorded the same degree of urgency as the treatment of cardiac arrest.

Introduction

It is generally accepted that the earlier thrombolytic treatment is given for acute myocardial infarction, the greater the benefit. Guidelines have been developed

and published recommending that thrombolysis should be given expeditiously.¹ But in developing policies for the speedy provision of thrombolytic treatment it is essential to know the magnitude of the benefit from earlier thrombolysis in relation to the difficulties experienced in expediting treatment. The benefit needs to be expressed as lives saved per hour of earlier treatment. The magnitude of the benefit of earlier thrombolysis can be determined ethically only with a trial in which patients are randomly allotted to receiving treatment on presentation, in the community, or later, after admission to hospital. Trials of this design are few and small in size; the three largest are the European myocardial infarction project (EMIP),² the myocardial infarction triage and intervention study (MITI),³ and the Grampian region early anistreplase trial (GREAT).⁴ Mortality after one month was not significantly reduced in any of these trials.

The objectives of GREAT were to assess the feasibility, safety, and efficacy of domiciliary thrombolysis by general practitioners. As this was a small trial, prehospital thrombolysis was not expected to show a significant reduction in mortality, and surrogate measures of efficacy were used. In order to maximise the time saving by domiciliary thrombolysis, and the likelihood of demonstrating its greater efficacy over hospital thrombolysis, participation was restricted to rural practices ≥ 26 km from the teaching hospital to which all cases were referred. Because the pre-hospital phase of the trial was conducted by general practitioners, delays in hospital were little affected by the conduct of the trial and were estimated at 87 minutes. As a consequence of this and the rural setting, the time saving by domiciliary thrombolysis in GREAT was substantial, at over two hours. As expected, prehospital thrombolysis did not result in a significant reduction in mortality at one month, but the mortality curves of home treated and hospital treated groups diverged during follow up, and the difference between them reached statistical significance by three months.⁴ At one year the absolute difference between mortality in home treated and