Zidovudine therapy in HIV infection: which patients should be treated and when

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Introduction

Zidovudine (3'-azido-3'-deoxythymidine; ZDV) is the drug of first choice in the treatment of patients with human immunodeficiency virus (HIV) infection. In common with other nucleoside analogue reverse transcriptase inhibitors (didanosine, ddI; zalcitabine, ddC; lamivudine, 3TC), ZDV has to be taken up by target cells, phosphorylated to the 5'-triphosphate by cellular enzymes and incorporated into target DNA. Drug effect is consequently dependent not only on dose and the rate of elimination from blood but on the rate and extent of phosphorylation. ZDV was first licensed for use in 1987 but many of the fundamental problems relating to clinical pharmacology remain unanswered. With 7 years experience of ZDV use it is also clear that the clinical benefit of ZDV therapy is limited and therefore the correct time for initiation of treatment is an important but controversial issue. This has been further highlighted with the recent publication of the Anglo French trial, Concorde. We review the clinical trials of ZDV therapy for various stages of HIV disease and how they may influence clinical practice.

ZDV therapy in AIDS and ARC

The efficacy of ZDV in the treatment of patients with the acquired immunodeficiency syndrome (AIDS) or AIDS related complex (ARC) was first reported in 1987 [1]. In this placebo controlled trial 282 patients were randomised to receive ZDV 1500 mg daily or matching placebo for a total of 24 weeks. Administration of ZDV resulted in a decreased mortality and halved the frequency of opportunistic infections. Significant drug toxicity resulted with this dose regimen, particularly bone marrow suppression producing anaemia (24%) and neutropenia (16%) with 21% of patients requiring multiple blood transfusions [2]. This prompted further studies using lower doses and treatment with ZDV 1200 mg daily reducing to 600 mg daily after 4 weeks, was found to be as effective as 1500 mg daily and was less toxic [3]. Another small study of short duration compared low (300 mg), medium (600 mg) and high (1500 mg) daily doses of ZDV in patients with ARC and found similar antiviral

activity [4]. A recent double-blind dose-response study of ZDV in 474 patients with AIDS or advanced HIV infection compared the efficacy and toxicity of 400 mg, 800 mg and 1200 mg ZDV daily [5]. There was no difference in survival between the treatment groups. Adverse effects of ZDV including anaemia and leucopenia were dose related and the time to first dose reduction was significantly longer with lower doses. The authors concluded that the ZDV dose should be limited between 400 and 600 mg daily in patients with advanced HIV disease. This reflects the current use of ZDV for the treatment of AIDS or ARC where the usual daily dose is 500 mg administered as 250 mg twice daily or alternatively as 100 mg five times daily.

Although ZDV therapy prolongs survival the median survival time is still less than 3 years from the time of diagnosis of AIDS [6–9]. Factors contributing to the loss of therapeutic benefit may include the acquisition of resistance to ZDV by HIV-1, cumulative ZDV toxicity, increased virulence of HIV-1 and increased virus burden resulting from loss of immune control of HIV-1 replication. Resistance to ZDV results from amino acid substitutions in the viral reverse transcriptase and develops more rapidly in patients with advanced disease. Following ZDV therapy for 12 months the majority of patients with AIDS or ARC will have ZDV resistant isolates as compared with 30% of those with early disease [10].

Early symptomatic HIV infection

Zidovudine may also be used in the treatment of patients earlier in the course of HIV infection. Administration of ZDV 1200 mg daily was compared with placebo in 711 patients with early symptomatic disease [11]. The progression to AIDS over a mean follow up time of 9 months was four times greater in the placebo group whilst the progression to AIDS or advanced ARC was approximately three times greater. Severe anaemia occurred in 5% of the ZDV group but not in the placebo group. The Veterans Affairs Cooperative Study Group compared the initiation of ZDV

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(1500 mg daily) early in the course of HIV infection, when patients were symptomatic and had CD4 lymphocyte counts between 200 and $500 \times 10^6 \text{ l}^{-1}$, with initiation later on when the CD4 count fell below $200 \times 10^6 \text{ l}^{-1}$ or AIDS had developed [12]. The mean follow up was over 2 years for the 338 symptomatic patients and AIDS developed in 28 patients in the early therapy group compared with 48 in the late therapy group. However, the number of deaths was similar (23 and 20 respectively), with a 3 year survival of approximately 80% for both groups. When an AIDS defining illness developed the patients in the early therapy group were more likely to have additional opportunistic infections and higher mortality. Early therapy was associated with more adverse effects including anaemia, leucopenia, nausea, vomiting and diarrhoea. Therefore both these placebo controlled trials of ZDV therapy in patients with early symptomatic HIV infection indicate that treatment reduces the rate of development of clinical AIDS by two to four fold but does not influence survival. The authors of the Veterans Affairs Study suggest that clinicians should consider delaying the initiation of ZDV therapy in patients whose clinical condition is stable and whose CD4 counts are between 200 and $500 \times 10^6 \text{ l}^{-1}$. This is a reasonable approach provided patients' symptoms are mild. For many patients prolonging the mildly symptomatic phase may be preferable to extending the period between the development of AIDS and death. Therefore ZDV therapy in early symptomatic HIV disease will require careful discussion with patients and decisions made on an individual basis.

Asymptomatic HIV infection

Four placebo controlled trials have examined the influence of ZDV treatment in asymptomatic patients. The first of these studies by the AIDS Clinical Trials Group (ACTG 019) compared high and low dose ZDV (1500 and 500 mg daily) with placebo to determine its safety and efficacy in delaying progression to symptomatic disease and prolonging survival [13]. The progression rate to AIDS and advanced ARC in patients with baseline CD4 counts less than $500 \times 10^6 \text{ l}^{-1}$ was halved in the high and low dose ZDV groups compared with placebo over the study period of 55 weeks. Severe anaemia (haemoglobin less than 8.0 g dl^{-1}) occurred in 6.3% and 1.1% of patients taking high and low dose ZDV respectively. In the 2 year follow up of the ACTG 019 study it was noted that the initial reduction in disease progression was lost for patients with CD4 counts less than $300 \times 10^6 \text{ l}^{-1}$ but persisted for those with CD4 counts greater than $300 \times 10^6 \text{ l}^{-1}$ [14]. The European Australian Collaborative Group published the results of two studies involving ZDV therapy in asymptomatic patients. The first of these investigated the effect of ZDV in 993 patients with asymptomatic HIV infection and CD4 counts greater than $400 \times 10^6 \text{ l}^{-1}$ who were randomised to ZDV 500 mg twice daily or placebo [15]. The primary endpoint was progression of disease as defined by the development of stage IV disease (e.g. opportunistic infections)

or two CD4 counts below $350 \times 10^6 \text{ l}^{-1}$. Following a median duration of 94 weeks, 26% of patients in the placebo group experienced disease progression (90% resulting from CD4 counts less than $350 \times 10^6 \text{ l}^{-1}$) compared with 15% in the ZDV group. If we consider the clinical endpoint, i.e. development of stage IV disease, then 4.4% of the placebo group and 2.2% of the ZDV group progressed over 2 years. The second European-Australian study (017) investigated the effect of ZDV 500 mg twice daily compared with placebo in 329 asymptomatic subjects with CD4 counts between 200 and $400 \times 10^6 \text{ l}^{-1}$ or if greater than $400 \times 10^6 \text{ l}^{-1}$ with HIV p24 antigenaemia ($>10 \text{ pg ml}^{-1}$) [16]. Treatment with ZDV significantly reduced the probability of developing symptomatic HIV disease and AIDS or ARC over the first 12 months. This benefit was not evident at 18 months or 2 years.

The Concorde study was a double-blind randomised comparison of two policies of ZDV therapy in 1749 asymptomatic HIV seropositive patients, i.e. ZDV 250 mg 6 hourly was administered immediately from the time of randomisation or deferred until the onset of AIDS, ARC or persistently low CD4 counts [17]. Prior to the development of AIDS or ARC, patients in the immediate group spent 81% of the study period on ZDV compared with 16% for the deferred group. There was no significant difference in clinical outcome between the two therapeutic policies. The 3 year estimated survival probabilities were 92% in the immediate and 94% in the deferred group. There was no significant difference in the progression of HIV disease, i.e. 3 year progression rates to AIDS or death were 18% in both groups and to ARC, AIDS or death were 29% for immediate and 32% for deferred groups. Consistent with results in asymptomatic HIV individuals there was an indication of an early but transient clinical benefit in favour of immediate treatment. There was a small but highly significant and persistent difference in CD4 counts between the groups but this was not translated into a significant clinical benefit. This may explain the apparent discrepancy between Concorde and conclusions from previous studies in asymptomatic HIV individuals where the endpoint, disease progression, was highly dependent on changes in CD4 count. With a daily dose of 1000 mg the frequency of severe haematological toxicity was low but greater in the immediate therapy group. The limited effect of ZDV on disease progression in asymptomatic patients must be balanced against drug toxicity, the demonstrated reduction in the quality of life [18], the emergence of ZDV resistance and the cost of therapy. The number of clinical endpoints (AIDS and death) in Concorde outnumber those in all other trials of ZDV in asymptomatic individuals. Therefore the results of Concorde do not encourage the early use of ZDV in symptom free HIV-infected adults. Many clinicians in the UK would now defer ZDV treatment until individuals develop symptomatic HIV disease or are thought to be at high risk of doing so, i.e. CD4 counts less than $200 \times 10^6 \text{ l}^{-1}$. Guidelines in the USA endorse both immediate and delayed ZDV therapy as reasonable alternatives for the management of asymptomatic patients with CD4 counts greater than $200 \times 10^6 \text{ l}^{-1}$ [19]. These strategies are reflected in the estimation by

Wellcome that 30% of ZDV sales in the USA during 1993 were for symptomless disease compared with 5% to 10% in Europe.

Paediatric HIV infection

Children under the age of 13 years represent approximately 2% of the total AIDS cases reported to the World Health Organisation. The clinical manifestations of HIV infection in children differ from those in adults. Lymphoid interstitial pneumonitis, parotitis and bacterial infections are more typical of HIV infection in children where disease progression is more rapid than in adults [20, 21]. Although there have been no controlled efficacy studies in children data from non-blind studies suggest clinical and immunological benefit with ZDV [22, 23]. Despite treatment, paediatric HIV infection remains a fatal disease and prevention is of paramount importance. Maternal-infant transmission is the primary means by which young children become infected with HIV [24]. It is estimated that between 15 to 40% of infants born to infected mothers become infected *in utero*, during labour and delivery or by breast feeding [25, 26]. Current evidence suggests that most maternal-infant HIV transmission occurs late in pregnancy or during labour [27, 28]. A recent study investigated the effect of ZDV therapy on maternal-infant transmission of HIV-1 in pregnant women with mildly symptomatic HIV disease [29]. This placebo controlled trial enrolled 477 HIV infected pregnant women (14 to 34 weeks gestation) with CD4 counts greater than $200 \times 10^6 \text{ l}^{-1}$. The ZDV regimen included antepartum ZDV 100 mg orally five times daily, intrapartum ZDV 2 mg kg^{-1} i.v. over 1 h then 1 mg $\text{kg}^{-1} \text{ h}^{-1}$ until delivery and ZDV for the new born 2 mg kg^{-1} 6 hourly for 6 weeks. The percentage of infants infected at 18 months was 8.3% in the ZDV group and 25.5% in the placebo group representing a 67% reduction in the risk of HIV transmission. This finding facilitates a major preventive effort, however the treatment may be less effective in patients with more advanced disease and those who have received long term ZDV therapy with associated resistant HIV strains [30].

Combination therapy and ZDV

Clinicians treating HIV patients who are unable to tolerate ZDV or whose clinical condition is deteriorating despite ZDV may change antiretroviral therapy to the

other nucleoside analogues, i.e. dideoxyinosine (didanosine; ddI) or dideoxycytidine (zalcitabine; ddC). These two compounds appears equally efficacious in delaying disease progression and death [31]. An alternative strategy is the use of combination drug regimens [32]. The potential advantage of such an approach includes the possibility for drug synergy, a reduction in toxicity and a reduction in the development of resistance. Therapeutic agents may also be targeted to act at different stages in the replicative cycle of the virus (e.g. ZDV plus a protease inhibitor) or at the same stage (e.g. ZDV plus ddI) [33]. Combination therapy with ZDV, ddI and ddC is based on additive effects of these agents against both ZDV sensitive and resistant virus as well as the largely non-overlapping toxicity profiles [34]. Studies of alternating and simultaneous regimes of ZDV and ddC suggested that a sustained anti-HIV effect could be obtained with reduced drug toxicity compared with ZDV monotherapy [35, 36]. Combination therapy with ZDV and ddI has also produced larger and more sustained increases in surrogate markers, e.g. CD4 counts, compared with ZDV alone and simultaneous therapy may be more beneficial than alternating drug regimens [37, 38]. The combination of ZDV and another reverse transcriptase inhibitor, lamivudine (3TC) appears promising. The ZDV plus 3TC combination produces a greater and more sustained effect on surrogate markers (CD4 count, cellular viraemia) than ZDV alone [39]. Therefore clinical studies of combination therapy are at an early stage but initial results are encouraging.

Conclusion

Zidovudine remains the antiretroviral agent of choice in the treatment of HIV disease. When administered to patients with AIDS or ARC it decreases mortality and reduces the frequency of opportunistic infections. In patients with early symptomatic HIV disease ZDV reduces the rate of development of clinical AIDS but does not influence survival. The results of Concorde do not encourage the early use of ZDV in asymptomatic HIV infected adults and many clinicians in the UK now defer ZDV treatment at least until patients develop symptoms. The exception to this approach is with HIV infected pregnant women when administration of ZDV during pregnancy reduces maternal-infant transmission of HIV-1. As ZDV therapy is not a cure and the beneficial effects are transient a strategy to overcome this has led to combination therapy and early results are encouraging.

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