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Didanosine treatment of haemophilic patients infected with HIV

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Summary. Twenty-six haemophilic patients with advanced HIV infection who had developed resistance or intolerance to zidovudine were treated with didanosine (ddI). 11 patients continue to take ddI at a median time of 14 months from commencement (range 7–18 months). Five of these patients showed an increase in CD4 lymphocyte count, reaching a maximum at a median time of 4 months. Four patients with HIV-related symptoms improved clinically. In general, the CD4 count and clinical improvements were not sustained. 11 patients discontinued ddI after a median of 3 months (range 3 days to 10 months), most commonly due to gastrointestinal side-effects. No case of pancreatitis or peripheral neuropathy was seen. Six patients, all with very advanced HIV disease, died. HIV-infected haemophilic patients who become resistant or intolerant to zidovudine may derive benefit from ddI, although this is usually transient.

Keywords: didanosine, HIV, haemophilia, reverse transcriptase inhibitors, CD4 lymphocytes.

The purine dideoxynucleoside analogue didanosine (2′,3′-dideoxyinosine; ddI) is a reverse transcriptase inhibitor with a mode of action similar to zidovudine [1]. It has been used in combination with, or as an alternative to, zidovudine in HIV-infected patients who are intolerant or resistant to this drug [2–4]. Patients with relatively advanced HIV disease on long-term zidovudine who are switched to ddI therapy develop new AIDS-defining events later than those who continue on zidovudine. An overall survival advantage has not been demonstrated, however, and the benefits of ddI treatment must be offset against the side-effects which include nausea, peripheral neuropathy and pancreatitis [4].

Although ddI is now licenced in the UK for the treatment of HIV disease either as an alternative or an adjunct to AZT, its role in the management of HIV infection remains to be fully determined.

We report our experience with ddI in the management of HIV-infected haemophilic patients attending haemophilia centres in Birmingham and Liverpool.

Patients and Methods

ddI was prescribed to 26 HIV-infected haemophilic patients aged 21–62, mean 36 years, attending the Merseyside and West Midlands Adult Regional Haemophilia Centres over a 2½-year period. 21 patients had severe haemophilia A (< 2% VIIIC), four moderate (< 15% VIIIC) and one mild (> 15% VIIIC). All patients had acquired their HIV infection from non-virally inactivated factor VIII concentrate.

Twenty-four patients were prescribed 250 mg ddI sachets b.d. Two patients were given reduced doses of 167 mg b.d. and 125 mg b.d. because of low body weight and advanced liver disease respectively. 13 patients were continued on zidovudine at 250 mg b.d. and one patient received monthly alternating courses of ddI and zidovudine due to zidovudine-related neutropenia. All patients continued on conventional pneumocystis and antifungal prophylaxis and received high-purity factor VIII concentrate preparations for bleeding episodes.

Patients were reviewed at least every 4 weeks for full clinical assessment, full blood count, CD4 count, and chemistry profile including serum amylase.

Results

The patients' characteristics, including the indication for ddI, mean CD4 count for each group at the beginning of treatment with ddI and the median length of time patients had been on zidovudine therapy are shown in Table 1. Two patients were changed to ddI because of intolerance

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Also, chronic HBV infection has been reported as responsible for many cases of chronic hepatitis amongst haemophilic patients [12]. In our study, only eight of 153 haemophiliacs examined were chronic carriers of HBsAg. It is, however, clear from our data that there is a correlation between previous HBV infection and a faster deterioration of liver function in HCV-positive haemophiliacs.

Hanley *et al.* [13] have described viral interference in haemophilic patients. This is the phenomenon where one virus reproduces inside a cell and inhibits or interferes with the subsequent infection by another virus; this is due to the antiviral action of cytokines induced by the first virus or to the fact that the two viruses compete for the use of the metabolic pathways of the host cell [14,15]. In a further study on anti-HCV seropositivity, confirmed by various second-generation tests in 76 patients with haemophilia, four chronic carriers of HBV infection were found to be anti-HCV positive, RIBA indeterminate and PCR negative [15]. We also found that the progression to liver insufficiency was faster in HIV-positive haemophilic patients, as described by Martin *et al.* [16].

Our results indicate that chronic hepatitis (persistent or active or cirrhosis) is universally present in our haemophiliacs, despite the fact that some were treated with lower doses of factor VIII or IX concentrates which had been defined by us at the beginning of the 1970s as being the minimum dose of coagulation factor concentrate capable of arresting bleeding [17].

Since the development of liver insufficiency is related to age, there will continue to be increasing morbidity and mortality amongst haemophilic patients. It is therefore important to identify on the basis of ALT levels, viral genotypes and HCV-RNA positivity [18,19] those patients who might benefit from interferon treatment.

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Table 1. Characteristics of 26 haemophilic patients treated with ddI. (Number of patients continuing on ddI in parentheses.)

Indication for ddI	*n*	Mean starting CD4 count ($\times 10^9$/l)	Median time on AZT (months)
Low CD4s on AZT	12 (4)	0.02 (< 0.01–0.05)	34 (18–49)
Falling CD4s on AZT	11 (6)	0.07 (0.05–0.19)	23 (9–36)
AZT intolerance	3 (1)	(see text)	(see text)
Whole group	26 (11)	0.05 (0.01–0.19)	25 (0–49)

to zidovudine due to immediate intolerable nausea and the third commenced on ddI and zidovudine sequentially due to severe neutropenia 17 months after starting zidovudine. The CD4 counts of these patients at the start of ddI therapy were 0.2, 0.04 and 0.08×10^9/l respectively. At the time of commencement of ddI, 12 patients were symptomatic of their HIV disease and seven of these had previously had an AIDS-defining illness. 18 patients had persistently elevated liver enzymes consistent with hepatitis C liver disease and three of these had clinical evidence of advanced liver disease.

Eleven patients continue to take ddI at a median time of 14 months from commencement (range 7–18 months). Figs 1 and 2 show the serial CD4 counts in these patients. Three of these patients continue to take zidovudine in combination with ddI. Two of the patients in the falling CD4 group (Fig. 1) and three in the very low CD4 group (Fig. 2) showed an increase in their CD4 count, reaching a maximum at a median time of 4 months after starting ddI. One of the former patients has sustained a CD4 increase from a pre-ddI level of 0.07×10^9/l for 17 months. As can be seen in the figures, rises in CD4 counts were generally not sustained and were particularly transient in those patients with very low counts. Four patients who were symptomatic of their HIV infection when ddI was commenced, in whom the CD4 count stabilized or increased following the start of therapy, improved clinically with weight gain, cessation of night sweats and an improvement in their wellbeing. This improvement was maintained for between 4 and 12 months in three patients who subsequently declined with progressive HIV related problems. One of these patients has developed intractable oral and oesophageal candida. The other eight patients remain well and none has developed an HIV-associated illness whilst on ddI.

Eleven patients discontinued ddI after a median of 3 months treatment (range 3 days to 10 months). The reasons for discontinuation of ddI were abdominal discomfort (three), intolerable diarrhoea (two), severe nausea (one), diabetes mellitus which settled spontaneously following cessation of ddI (one), sleep disturbance (one) and refusal/compliance (one). Two patients developed a severe acute hepatitis superimposed upon chronic hepatitis C. This followed an alcoholic binge in both patients. Although all medication, including ddI, was discontinued it was thought unlikely that the hepatitis was drug induced in either patient. The acute hepatitis settled fully in both patients. One patient declined to restart ddI and the other has been unable to tolerate further ddI due to associated severe lethargy.

ddI intolerance was not restricted to patients with advanced HIV disease although there was a tendency for this group of patients to be less tolerant to ddI than

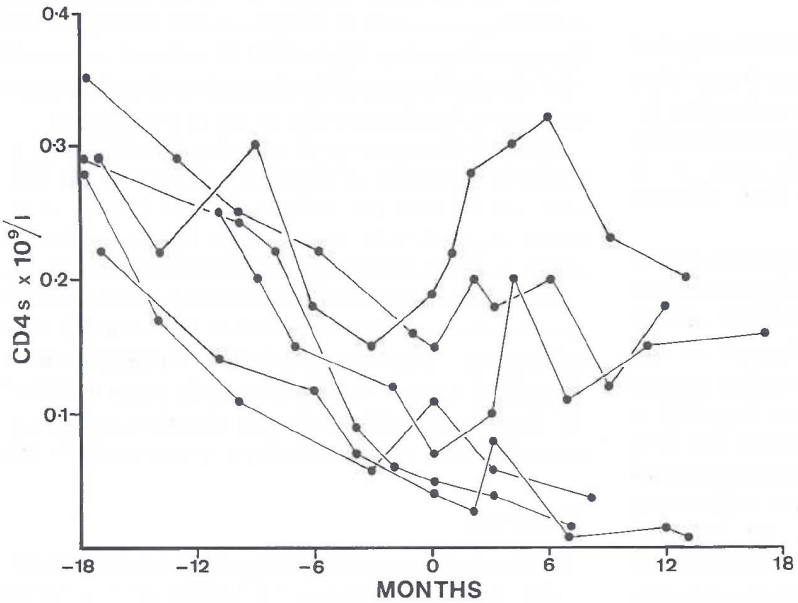

Fig. 1. Serial CD4 lymphocyte counts in patients continuing on ddI with falling counts on zidovudine as the indication for ddI therapy. Zero time point indicates commencement of ddI.

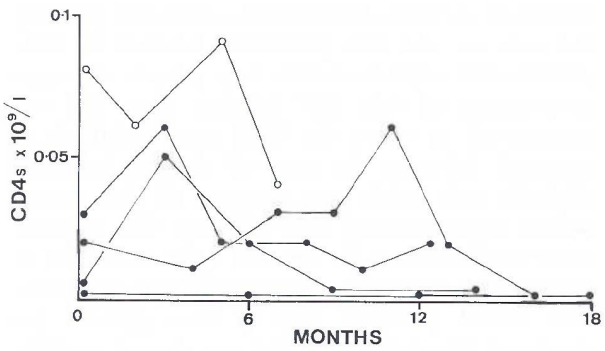

Fig. 2. Serial CD4 lymphocyte counts in patients continuing on ddI with low counts at the commencement of ddI (closed circles) and in the patient with zidovudine induced neutropenia (open circles). Zero time point indicates commencement of ddI.

asymptomatic patients. No patient developed peripheral neuropathy, biochemical or clinical evidence of pancreatitis or bone marrow suppression. All patients with persistent neutropenia or thrombocytopenia had advanced HIV disease and their cytopenias were probably HIV- rather than drug-related. None of the patients who discontinued ddI showed any improvement in CD4 counts during the relatively short period of time they were taking the drug.

Six patients, all with very low CD4 counts, have died from HIV disease. In four of these ddI was discontinued just prior to death after 4, 9, 12 and 12 months treatment respectively. In the remaining two patients ddI had been discontinued after 5 months in both due to intolerable abdominal discomfort, 5 and 7 months prior to death respectively.

Discussion

The HIV reverse transcriptase inhibitor didanosine, used alone or in combination with other reverse transcriptase inhibitors, is an alternative therapy to zidovudine for HIV-infected patients intolerant or resistant to zidovudine [5]. We report our experience of this agent in 26 haemophilic patients, all of whom had relatively advanced HIV infection.

A significant increase in CD4 levels has previously been observed in patients treated with ddI during the first few months of therapy followed by an eventual gradual decline presumably due to the development of ddI resistance [5–7]. Two of our patients showed an increase in CD4 count, more than doubling in one from 0.07 to 0.2×10^9/l. In this patient the improvement has been sustained for over 17 months and has been accompanied by resolution of night sweats and diarrhoea and recovery of weight lost before treatment with ddI began. A transient increase or stabilization of the CD4 count was observed in other patients. This was sometimes accompanied by clinical improvement which again was usually transient, only lasting several months. The recurrence of symptoms in these patients may reflect the development of ddI resistance, although there is as yet little evidence to suggest that the emergence of ddI-resistant HIV genotypes with an accompanying fall in CD4 counts is associated with clinical progression [7]. A more sustained response may be obtained with reverse transcriptase inhibitors used sequentially or in combination, because these approaches may modify the development of resistant HIV strains.

All six patients who died had been on long-term zidovudine therapy and had very low CD4 counts. Five had an AIDS-defining illness before ddI therapy began. ddI may be of limited value in patients with very advanced HIV disease.

Seven patients had to discontinue ddI due to unacceptable side-effects which recurred on rechallenge and were therefore considered attributable to the drug. Gastrointestinal disturbances were the most frequent side-effects, in common with other trials [2]. One patient with advanced hepatitis C developed symptomatic diabetes mellitus which settled completely on cessation of ddI, suggesting that this was drug-related. This may have been induced by a direct drug effect on the pancreas. ddI is recognized to cause deranged liver function and it is not possible to exclude ddI as a contributing factor in the acute hepatitis following excessive alcohol intake in two of the patients. We would recommend that liver function tests are monitored closely in HIV seropositive haemophilic patients on ddI due to the high prevalence of accompanying hepatitis C infection. We suggest that reduced doses of ddI should be prescribed to patients with clinically advanced liver disease.

The use of lower dosage of ddI as recommended following publication of the preliminary findings of the European/Australian Alpha trial [9] was not associated with the development of biochemical or clinical pancreatitis or peripheral neuropathy in any of our patients.

Although the incidence of side-effects was high, this is probably a reflection of the advanced nature of the HIV infection amongst our patients. Patients treated at an earlier stage of their disease might expect fewer side-effects, as has been the experience with zidovudine [8,10].

This study suggests that symptomatic patients resistant to zidovudine may derive benefit from the use of ddI, used either alone or in combination, but that the benefit is often short-lived. Patients with CD4 counts in excess of 0.05×10^9/l may be more likely to benefit than those with lower counts, but this can only be established by a controlled trial.

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