

5th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV



8–11 July 2003, Le Meridien Montparnasse, Paris, France

ANTIRETROVIRAL THERAPY WITH DIDANOSINE, STAVUDINE AND ZALCITABINE IS ASSOCIATED WITH DEPLETION OF MITOCHONDRIAL DNA IN THE LIVER

Antiviral Therapy 2003; 8:L15 (abstract 17)

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OBJECTIVES: *In vitro* data suggest that nucleoside analogue reverse transcriptase inhibitors cause depletion of mitochondrial DNA (mtDNA) in liver by inhibiting polymerase- γ , which may contribute to clinical hyperlactataemia.

METHODS: In a cross-sectional study, liver was biopsied from consecutive individuals willing to give informed consent. A total of 111 individuals were biopsied for reasons of diffuse liver pathology, elevated liver enzymes or active hepatitis C (HCV). Seventeen patients were HIV-negative/HCV-negative, 14 were HIV-negative/HCV-positive. Among the 80 HIV-positive/HCV-positive patients, 11 had no antiretroviral therapy at the time of biopsy, 34 were receiving at least one D-drug (zalcitabine, didanosine, stavudine) and 35 were treated without D-drugs. Liver histology was graded by a single blinded pathologist; liver mtDNA was quantified by Southern blot. Mean levels of mtDNA and lactate among groups were compared using *t*-test or Mann-Whitney rank sum test, as appropriate.

RESULTS: Compared to HIV-negative/HCV-negative individuals, mtDNA was reduced to 81% ($P=0.03$) in HIV-negative/HCV-positive patients and to 71% ($P=0.02$) in HIV-positive/HCV-positive individuals currently without antiretroviral therapy. This effect may be due to cirrhosis, as a high fibrosis score was associated with mtDNA depletion. Among HIV-positive/HCV-positive patients, mtDNA was reduced ($P<0.001$) to 60% in D-drug treated, compared to HIV-positive/HCV-positive/antiretroviral therapy-negative individuals, but not (114%, $P=0.56$) in those without D-drugs. Lactate was increased by

170% ($P=0.017$) in the D-drug group and by 142% ($P=0.042$) in the non-D-drug group, whereas fibrosis and activity scores did not differ. Within the HIV-positive/ HCV-positive category treated with D-drugs as part of the current HIV-therapy, 24 subjects received only stavudine, two only didanosine, two only zalcitabine, and six a combination of both didanosine and stavudine. Compared to untreated patients mtDNA was diminished to 67% (stavudine, $P=0.006$), 51% (didanosine), 50% (zalcitabine) and to 41% (stavudine plus didanosine, $P<0.001$). Current use of zidovudine, lamivudine or abacavir was not associated with significant mtDNA depletion. Groups did not differ with regard to age, time on current antiretroviral therapy, and key virological and immunological parameters. mtDNA deletions were not observed.

CONCLUSIONS: Current treatment with didanosine, stavudine or zalcitabine is associated with decreased mtDNA in liver irrespective of cirrhosis and inflammation. This may be an important, but not exclusive, factor contributing to hyperlactataemia.

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2003-07-08
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