



8th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV

San Francisco, California - September 24 - 26, 2006

A 6-MONTH ART INTERRUPTION IN HIV-INFECTED PATIENTS IMPROVES ADIPOSE TISSUE MORPHOLOGY: AND GENE EXPRESSION (ANRS EP29 LIPOSTOP)

Antiviral Therapy 2006; 11:L6 (abstract no. 5)

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This study was performed to determine whether adipose tissue parameters were modified after a 6-month ART interruption in well-controlled HIV-infected patients. Forty patients were included and 33 completed the study. Clinical and biological evaluation and needle biopsy of subcutaneous abdominal adipose tissue (AT) were performed at inclusion and after 6 months (M6). At M6, clinical parameters were not significantly modified. AT morphology was evaluated in 29 patients (10 under PI+NRTIs, 19 NRTIs without PI, 5 under stavudine, 12 zidovudine and 12 other NRTIs at inclusion); mitochondrial DNA in 23 patients and adipose tissue gene expression in 20 patients (8 under PI+NRTIs, 12 under NRTIs without PI, 1 under stavudine, 8 zidovudine and 11 other NRTIs). Overall, the level of fibrosis was not modified at M6. By contrast, AT inflammation was markedly improved showing a decrease in the number of lipogranulomas and macrophages and in that of cells stained for TNF- α or IL6. The number of cells positive for TNF- α or IL6 cells was significantly increased at inclusion in patients under stavudine or zidovudine but not under other NRTIs. Inflammation was also reduced at the molecular level as indicated by decreased CD68 mRNA, a macrophage marker. Mitochondrial alterations observed in AT were improved at M6 in patients stopping thymidine analogues as shown by decreased COX4 mRNA and increased mtDNA and COX2/COX4 ratio. In these patients, differentiation of AT improved since SREBP-1 mRNA was increased. In patients stopping PIs, the expression of markers of adipocyte differentiation and mitochondrial biogenesis were improved (PPAR- γ , PGC1- α , COX2). Taken as a whole,

we show here that a 6-month treatment interruption markedly improved adipose functions. Stavudine and zidovudine were mainly involved in AT inflammation, which recovered after stopping these drugs. They also play a role in mitochondrial and differentiation alterations. PIs were also involved in differentiation and mitochondrial alterations although at different levels. These data clearly outline the deleterious impact of ART on adipose tissue with a prominent role for thymidine analogues. Since adipose functions recovered after a 6-month interruption, switch or treatment modifications strategies are justified.

2006-09-24

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