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Clinical Science Workshop 5

Antiretroviral therapy

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Mitochondrial morbidity and perinatal exposure to nucleoside analogues

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The efficacy of antiretroviral treatment to prevent the transmission of HIV-1 from mother to child has been established but tolerance of this treatment remains to be assessed on a large scale and in the long term. In a pilot study we described 8 children presenting neurological symptoms compatible with persistent mitochondrial dysfunction (Lancet, 1999, 354: 1084–89). The aim of the present work was to determine the symptoms, the frequency and the risks factors for symptoms consistent with mitochondrial dysfunction in children born to HIV-seropositive mothers including both those exposed and not exposed to anti retroviral drugs during perinatal period. We performed an exhaustive study using a predetermined algorithm of the unexplained clinical and biological symptoms consistent with mitochondrial dysfunction among children not infected with HIV in which 2644/4412 were perinatally exposed to antiretroviral in the large french pediatric prospective cohort. Detected cases received complementary radiological, enzymological and pathological analyses. We observed that febrile seizures were more frequent in exposed children (Lancet 2002; 359:583–584). The same was true for abnormal cerebral MRI findings. Finally, 7 among the 4412 evaluated children had demonstrated mitochondrial dysfunction (plus 5 notified cases corresponding to children not included in the cohort. All were perinatally exposed to anti retroviral drugs. 14 other children in the cohort, all of whom were exposed to anti retroviral drugs had a possible, but not yet demonstrated, mitochondrial dysfunction.

In conclusion: Children exposed to nucleoside analogs during the perinatal period appear to be at risk of presenting symptoms associated with persistent dysfunction of the mitochondrial respiratory chain.

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Resolution and prevention of FIV-induced neurological deficits by treatment with the protease inhibitor TL-3

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Using comparative structural and enzymological analyses between HIV-1 and FIV proteases, we have synthesized a series of inhibitors that exhibit broad efficacy and are less susceptible to resistance development. This effort has resulted in the development of TL-3, which is efficacious against FIV, SIV, and HIV virus replication, in vitro. We now report that oral administration of TL-3 (2×20 mg/day), to cats prevents the onset and/or progression of FIV-induced CNS functional pathology. Four experimental groups of feline subjects were studied (N = 4/group):1. TL-3 only; 2. FIV only; 3. FIV + TL-3; and, 4. Control. Auditory brainstem evoked potentials (BAERs), a functional measure of the progression of FIV-induced CNS disease, were measured every 14 days. FIV infection alone led to an increased latency in the BAER P4 wave measured 14 days after the infection. In the FIV + TL-3 treatment group, TL-3 was administered per os two days prior to the FIV infection. BAER abnormalities never developed in this group even after the termination of TL-3 treatment (two months post). Interestingly, in the FIV alone treatment group, TL-3 treatment initiated three months after FIV-infection resulted in a reversal to normal P4 latencies within 14 days during treatment. TL-3 was then stopped in this group and the P4 delay recurred after three weeks, suggesting a transient efficacy of the drug. . Early (one month) analyses of viral antigen expression by PCR analyses showed lower virus levels in the DNA of PBMCs from TL-3-treated cats. However, over the course of the experiment we noted fluctuations in viral load in the periphery independent of TL-3 treatment, typical of results using a monotherapeutic regimen. These findings indicate that a rationally designed protease inhibitor, given by mouth, is affective in suppressing FIV infection and functional disease progression.

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Effects of antiretroviral drugs on the dynamics of HIV replication in human brain tissue

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Background: Cognitive impairment and HIV associated dementia (HAD)correlates with neuronal damage and death and rising viral burden both in brain and cerebrospinal fluid. Thus, brain protection would require both prevention of neuronal loss and suppression of viral load. However the suppressive effects of the various antiretroviral drugs on brain viral replication is not fully understood. Method: we addressed this issue by utilising a human brain tissue aggregate system, which is the nearest to the *in vivo* situation. Aggregates consisted of all the relevent cell types; neurons, astrocytes, oligodendrocytes and microglia/macrophages and neurotransmitters. Following four weeks establishment, aggregates were infected with the macrophage tropic strain SF162 (at 1:10 dilution of stock), in some stavudine at 0.3 uM, zidovudine at 2 nM or 20 pM or abacavir at 300 nM or 3 nM were added either prior to, simultaneously or after infection. Results: viral replication was demonstrated by p24 ELISA. Viral replication for the three drugs stavudine, zidovudine and abacavir were observed. Pre-treatment with stavudine considerably reduced the rate of increase in viral replication (univariate analysis of variance, $p = 0.013$), whilst simultaneous and post additions produced higher levels of p24. However, the rate of viral replication for both zidovudine and abacavir was not statistically significant. Conclusion: all three nucleoside reverse transcriptase inhibitors were utilised at levels observed in the CSF and within the IC50 range. Viral replication was affected by the time of addition of stavudine in relation to infection. This was not apparent for zidovudine and abacavir.

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Therapeutic decision-making in Neuro-AIDS

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Background: The central nervous system (CNS) is one major target and can serve as a sanctuary site for HIV-1. HIV-1 associated minor motor deficits (MMD) have proven to be a sensitive predictor of HIV-1 associated dementia, AIDS and death, which is independent of CD4 cells and HIV-1 plasma and cerebrospinal fluid viral load. This abstract proposes a neurological therapeutic rationale.

Patients: Out of 2249 HIV1+ patients (consecutively seen between 01/1988 and 01/2002) we selected those therapy-naïve patients who manifested HIV-1 associated minor motor deficits and who were then switched to defined antiretroviral therapy regimens including nucleoside analogues only (NA), and additional protease inhibitors (PI) (either indinavir IND, or saquinavir SQV) or one non-nucleoside analogue (NNRTI) inhibitor of HIV-1 reverse transcriptase (either efavirenz EFV, or nevirapine NVP).

Methods: HIV-1 associated MMD were quantified by contraction times (CT; msec) in patients at months 0 (therapy switch) and 6 months later. Z-scores were calculated and the differences analysed for this treatment period.

Results: In contrast to untreated patients, NA treatment combinations including either zidovudine or stavudine lead to a similar and significant improvement of z-scores over an observation period of 6 months (AZT alone: +1.353 ($n = 115$); AZT + 2nd NA: +1.344 ($n = 48$); D4T + 2nd NA: 1.526 ($n = 8$)). Both PI do not further improve this performance, whereas the additional use of NVP showed the best results (NVP + 2 NA: +2.342 ($n = 9$)) in patients untreated so far.

Conclusions: In patients with HIV-1 associated MMD combinations including a NNRTI may be the first choice, whereas HAART including PI may be the first choice in patients with high plasma viral load, but without HIV-1 associated MMD. In those patients, NNRTI could then be used, if they develop HIV-1 associated MMD under treatment with PI.