

Developing tools for investigation of mitochondrial toxicity in the clinical setting

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Dr. Nolan discussed mitochondrial toxicity research in the context of the clinical setting, where clinical data from a well-characterised observational cohort can be utilized to inform basic science research. The clinical aspects discussed were the lipodystrophy syndrome and lactic acidosis/hyperlactataemia, while the discussion of mitochondrial toxicity research focused on the development of investigational methods of appropriate sensitivity and reproducibility. In examining the possibility that lipodystrophy represents a mitochondrial toxicity, Dr Nolan proposed that clinical data could contribute through addressing a number of questions:

- Do NRTIs contribute to the syndrome, and are these drugs sufficient to cause the syndrome?
- Are there differences between NRTIs in relation to the risk of developing the syndrome?
- Does the risk of developing lipodystrophy correlate with risk of developing other mitochondrial toxicities, particularly hyperlactataemia.

Dr. Nolan outlined the history of the lipodystrophy syndrome, and its temporal relationship to the introduction of protease inhibitors as well as to stavudine. He distinguished two components of lipodystrophy: (1) changes in fat distribution, including subcutaneous fat wasting and intra-abdominal or localized fat accumulation, and (2) metabolic complications including dyslipidemia, insulin resistance, and (rarely) diabetes, indicating that there is increasing evidence that these endpoints should be considered separately. Fat distribution abnormalities have been associated with nucleoside reverse transcriptase inhibitors (NRTIs), and it has been demonstrated that NRTIs are sufficient to cause these changes in the absence of PIs. Metabolic complications, on the other hand, have been more strongly associated with protease inhibitors (PIs), and occur in the absence of body composition changes.

While NRTIs are sufficient to cause subcutaneous fat wasting, the addition of PI therapy accelerates subcutaneous fat wasting compared with patients taking only NRTIs, and in the clinical setting it is PIs that are 'dominant' in contributing to fat wasting.

In addition, results from the Western Australian cohort indicate that the risk of subcutaneous wasting among people taking stavudine (d4T) was about twice that of people taking zidovudine (AZT), a finding confirmed in other cohort studies. These analyses have also confirmed a link between increased risk of lipodystrophy with host factors such as older age and white race.

The contribution of NRTIs to subcutaneous fat wasting is also supported by the results of studies in which a PI has been replaced with a nonnucleoside reverse transcriptase inhibitor (NNRTI) or with the NRTI abacavir. In general, a switch to the NNRTI efavirenz had modest effects on metabolic profiles and little or no effect on lipoatrophy. Switching to the NNRTI nevirapine, or to abacavir, had a greater impact on metabolic profiles than did switching to efavirenz, but again there was little change in lipoatrophy. A study by Thierry Saint-Marc in which AZT replaced d4T found improvements in lipoatrophy after the switch, but the study was nonrandomized. A randomized study is now being done to test Saint-Marc's results.

Dr Nolan concluded that there is an established role for NRTIs in the pathogenesis of subcutaneous fat wasting and fat composition changes, and that this effect was most apparent with stavudine use. NRTIs are also associated with hyperlactataemia, a marker of mitochondrial dysfunction. While protease inhibitors are strongly and independently associated with the metabolic syndrome, they interact with NRTIs to compound subcutaneous fat wasting.

Dr. Nolan proposed that the synergistic effect of NRTIs and PIs on adipose tissue could be explained either by a divergent model, in which NRTIs and PIs independently affect fat, or by a convergent model, in which NRTIs and PIs affect fat through a common pathway. Given the possibility that PIs may enhance mitochondrial toxicity as a 'final common pathway' of pathogenesis prompted further clinical studies examining the role of PI use in hyperlactataemia, a recognized marker of systemic mitochondrial dysfunction.