Hot News

Welcome to «Hot News», a section of AIDS Reviews written by the editors and invited experts which focuses on recently reported information believed to be of both impact and higher interest to the readership.

Can the inhibitory quotient (IQ) be useful in clinical practice?

Two recent reports support the predictive value of the inhibitory quotient (IQ) for virologic response to antiretroviral therapy (Casado et al. AIDS 2003; 17:262-4; Shulman et al. Antimicrob Agents Chemother 2002;46:3907-16). IQ is a measure that integrates both resistance and drug levels. It is usually expressed as the ratio of Ctrough/IC50, where IC50 can be derived from real phenotype or a phenotypic interpretation of the genotype (when a virtual phenotype is used, then often is referred as virtual or vIQ). Casado et al., reported results using dual PI combinations (with NRTI) in heavily pretreated patients. The virologic response at 3 months was significantly better among patients with an IQ greater than 1 for nelfinavir and saquinavir (27 patients on dual nelfinavir/saquinavir therapy). The results were similar for indinavir and ritonavir (25 patients on this dual PI therapy, pooling 400/400 mg dosing and 800/100 mg dosing), but those results were only borderline significant. In some way it is surprising that such a low IQ (PI trough concentrations were higher than those needed to inhibit only 50% of the virus replication) were still sufficient to provide a significant viral load drop. In many cases, achievement of higher IQ values may be unrealistic in such a population with pre-existing resistance to PIs.

Shulman et al. reported vIQ being a better predictor for virologic response than either virtual phenotype or drug exposure separately. They examined 37 patients switched from indinavir/ritonavir 800/100 mg tid to 400/400 bid, which increased indinavir plasma levels. A significant better virologic response was observed with indinavir vIQ above 2, even when ritonavir vIQ was reduced dramatically. Since this study was an intervention study designed to boost indinavir levels, it proves that increases in drug levels may overcome the limited response seen in patients with some PI resistance at baseline. If this is best done using the parameter IQ or vIQ, or whether other combinations of measures of resistance and drug levels may be used with similar benefit, still needs to be investigated.

Genotypic resistance testing is more easily available than phenotypic measurements. Since vIQ is in fact a complex interpretation of the genotype, one could imagine other ways than IQ or vIQ to take resistance into account together with drug levels. Much still needs to be determined on optimal ways to interpret drug levels, as well as resistance. A useful overview on pharmacokinetics of antiretrovirals has been performed by Acosta et al. (Clin Inf Dis 2003;36:373-7), together with suggestions on how to use drug levels in combination with information derived from phenotypic drug resistance. Many studies considering both types of data are currently being set up. The years to come will certainly be of much interest to see how drug levels and resistance are integrated into clinical practice. Besides, taking into account drug adherence will be even a greater challenge.

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Pathogenesis of HTLV-associated myelopathy

HTLV-I infects around 15 million people worldwide. Only 3% of HTLV-I-infected persons develop a subacute neurological disease named Tropical spastic paraparesis (TSP) or HTLV-I-associated myelopathy (HAM). Whereas there is no doubt that immune-mediated phenomena are involved in the production of TSP/HAM, the specific mechanisms have been unclear until recent times. During the last year, two main hypotheses have been postulated for the pathogenesis of HAM/TSP. The first suggest that molecular mimicry could be involved (Levin et al. Nature Med 2002;8:509-13). Autoantibodies generated against HTLV-I tax protein could also react against nnRNP-A1, a nuclear protein localized in the central nervous system within Betz cells, the motoneurons of the cortex which produces the pyramidal tract in the spinal cord. Axonal loss is responsible for the persistent disability characterized by spastic paraparesis and urinary disturbance.

The second hypothesis is mainly based on histological findings found after the exam of the spinal cord of patients who died with HAM/TSP. A rich infiltration of the spinal cord by CD8+ T-lymphocytes is often seen in those patients, suggesting that cellular immunity play an important role in the pathogenesis of HAM/TSP (*Jacobson. J* Infect Dis 2002;186(suppl 2):187-92). A high proviral load in both CD4+ and CD8+ cells could be the first trigger to drive a higher expression of HTLV-I antigens. As

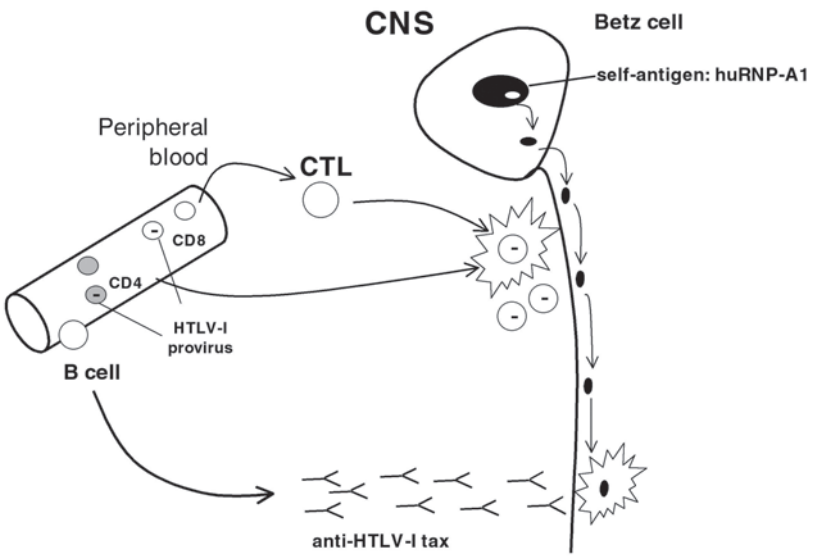

Figure 1. *Pathogenesis of TSP/HAM*

the HTLV-I proviral load is uniformly greater in the cerebral spinal fluid (CSF) than in peripheral blood, inflammatory reactions driven by CD8 cytotoxic T lymphocytes (CTL) develop against infected cells expressing HTLV-I antigens, preferentially within the central nervous system.

Based on these studies, the pathogenesis of HAM/TSP seems to involve both humoral and cellular immune responses against HTLV-I associated antigens (Osame J. NeuroVirol 2002;8:359-64). In this context, large HTLV-I loads as seen often after transfusion of HTLV-I contaminated blood or after transplantation of organs from asymptomatic HTLV-I carriers may prone recipients to develop HAM/TSP more frequently. This seem to have been the case in a recent report (Toro et al. Transplantation 2003;75:102-4) in which all three organ recipients developed HAM/TSP shortly after transplantation of organs from an unknown HTLV-I carrier.

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Erratum

Schmidt B, Walter H, Zeitler N and Korn K.
Genotypic Drug Resistance Interpretation Systems - the Cutting Edge of Antiretroviral Therapy.

AIDS Rev 2002;4:148-56.

Table 1 does not differentiate properly between non-commercial, freely available interpretation systems and the commercial web sites that offer sequence analyses using these interpretation systems. All of the interpretation systems used by the ABL networks web site were developed by non-commercial scientific groups. In addition, the ANRS interpretation system (http://www.hivfrenchresistance.org) as well as the Rega algorithm are freely available to the public. The authors apologize for this misunderstanding.