Management of antiretroviral-related neuropsychiatric adverse effects

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With the advent of highly active antiretroviral therapy (HAART), there has been a dramatic decrease in AIDS-related mortality and morbidity (1). Undetectable viral load is often achieved and long term viral suppression maintained, especially in treatment-naïve patients. Immune reconstitution is seen, as demonstrated by increased CD4 counts, the delay in progression to AIDS and a decrease in opportunistic infections.

Despite the efficacy of HAART regimens, antiretroviral therapy often causes significant toxicities, ranging from mild, self-limiting symptoms to serious long term adverse effects. Antiretroviral-related side effects will adversely affect the patient's adherence to medication regimens. Surveys of patients receiving HAART have shown that approximately one-third of the patients missed doses within the previous three days and that side effects accounted for 10% to 15% or more of those treatment discontinuations (2). Poor adherence is strongly associated with virological failure of potent antiretroviral therapy. It has been demonstrated that a greater than 95% adherence is required for HAART viral suppression maintenance (3). Because HAART is a life-long therapy, physicians are faced with the challenge of selecting a regimen that the patient can comply with. In addition, the clinician needs to manage any treatment-related side effects and support the patient in maintaining adherence.

One of the most well recognized examples of long term toxicities is the lipodystrophy syndrome – characterized by fat redistribution and metabolic disturbances such as hypertriglyceridemia, hypercholesterolemia, insulin resistance and diabetes mellitus (4,5). Lipodystrophy, despite its still unknown pathogenesis, is closely associated with the use of

protease inhibitors (PIs). It has been reported that up to 83% of PI-treated patients exhibited lipodystrophy syndromes (6). The lipodystrophy syndrome not only has a severe psychological impact on patients due to visible changes in body shape, but the associated lipid changes may result in an increased risk for ischemic heart disease (4). Recently, mitochondrial toxicity seen with the use of nucleoside reverse transcriptase inhibitors (NRTIs) has been suggested to play a role in lipodystrophy. Mitochondrial toxicity is thought to result in many of the medium and long term toxicities seen with NRTIs. The toxicities include myopathy, neuropathy, hepatic steatosis, lactic acidemia, pancreatitis and, possibly, lipodystrophy (4).

Other well-known toxicities of antiretroviral agents are diarrhea and nausea, which are frequently encountered with PIs (4,5). Rash has been observed with all non-nucleoside reverse transcriptase inhibitors (NNRTIs), the NRTI abacavir and the PI amprenavir, and is less common with the other NRTIs or PIs. Various neuropsychiatric symptoms such as headache, insomnia, dizziness, sleep disturbances or seizures have been associated with all antiretroviral agents. However, neuropsychiatric symptoms are more frequently encountered with efavirenz, an NNRTI, and NRTIs such as zidovudine and lamivudine (5,7).

Efavirenz is an effective antiretroviral agent listed among the strongly recommended agents within the United States Department of Health and Human Service Guidelines for the treatment of HIV infection (8). It is generally well tolerated, with minimal long term toxicities. The most frequent side effects are nervous system symptoms (dizziness, insomnia, somnolence, impaired concentration, vivid dreams), and

these symptoms are usually mild to moderate (9). The symptoms are usually self-limiting and resolve after the first two to four weeks of efavirenz use. In clinical trials, nervous system symptoms occurred in 53% of efavirenz-treated patients and accounted for 2.1% of treatment discontinuation. To date, the mechanism for efavirenz-related nervous symptoms has not been elucidated. Although efavirenz penetrates into various key viral sanctuaries including the cerebral spinal fluid, 58 binding assays of various central nervous system neurotransmitters in laboratory assays have not demonstrated efavirenz binding of clinical significance to specific neurotransmitter receptor sites (10).

In addition to nervous system symptoms, patients less frequently report a variety of psychiatric adverse events. In controlled trials, the frequency of specific serious psychiatric events among efavirenz patients and control regimens were, respectively: severe depression (1.6%, 0.6%); suicidal ideation (0.6%, 0.3%); nonfatal suicide attempts (0.4%, 0%); aggressive behaviour (0.4%, 0.3%); paranoid reactions (0.4%, 0.3%); and manic reactions (0.1%, 0%) (9). Data from the Efavirenz North American Expanded Access Program confirm the relatively rare frequency of the serious or severe psychiatric events (grades 3/4) observed in clinical trials. Of the 7842 patients, there was a reported 0.36% incidence of severe or serious depression (10).

To date, efavirenz has not been demonstrated to be associated with the lipodystrophy syndrome (11). However, considering that efavirenz is a relatively new agent, a conclusion at this time may be premature. Compared directly with a PI-based regimen, efavirenz demonstrated equal if not superior viral suppression with a better tolerability profile in treatment-naïve patients (12,13).

In a similar retrospective review conducted in several HIV clinics (10,14), it was found that the discontinuation rate due to neuropsychiatric side effects varied widely among the participating clinics. This may reflect the varied practice of clinics across Canada in terms of documenting and monitoring for side effects, as well as the individual physician's comfort level or persistence in the management of neuropsychiatric symptoms related to efavirenz. Needs assessment surveys among health professionals (physicians, pharmacists) and patient groups (AIDS service organizations, patients) revealed that there is a need for information and practical tools to manage these treatment-emergent symptoms (10).

To this effect, we convened a panel of experts to provide information and discuss the issues of appropriate management of antiretroviral-related neuropsychiatric symptoms at a meeting held December 4, 2000. Funding for the meeting was provided by DuPont Pharma Inc. In the present supple-

ment, the management of these symptoms as related to HIV and antiretroviral agents is described (page 9C-19C). Finally, the consensus recommendations arrived at by the panel on the management of efavirenz-related side effects are presented (pages 20C-30C).

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