Hot News

Rosuvastatin – The Most Potent and Less Toxic Statin for HIV Patients

Cardiovascular complications have emerged as an important cause of morbidity and mortality in HIV-infected individuals in the Western world, where antiretroviral therapy has halted progression to advance immunodeficiency and development of classic opportunistic illnesses. For this reason, prevention of metabolic abnormalities associated to increased risk of myocardial infarction and stroke have recently attracted much attention in routine HIV care. In this regard, proper management of dyslipidemia and glucose abnormalities is being addressed more intensively in a growing number of patients.

Up to one-third of HIV individuals on antiretroviral therapy may show high cholesterol and/or triglycerides. Lipid disorders can be tackled with diet and exercise, but often require the prescription of specific drug therapy. Statins are by far the most common agents used to reduce cholesterol. A recent study has retrospectively examined the performance of different statins to manage dyslipidemia in 700 HIV patients in the USA (Singh, et al. Clin Infect Dis. 2011;52:387-95). Overall, at one year up to two-thirds of patients reached NCEP goals for LDL-cholesterol and/or non-HDL-cholesterol, the success being two-fold greater with rosuvastatin or atorvastatin than with pravastatin. Discontinuation of statins was made in 6.4% of patients, being slightly higher with atorvastatin (7.3%) than rosuvastatin (5.3%). Increases in muscle enzymes (CPK, creatine phosphokinase) and liver enzymes were the most common lab abnormalities in patients experiencing side effects with statins.

The study had several limitations, including the fact that the effects of diet, exercise, concomitant use of ezetrol, dosing of statins, fasting and antiretroviral treatment modality were not taken into account. However, the large number of patients examined reinforces the robustness of the results. The fact that rosuvastatin is not associated with relevant drug-drug interactions in contrast with other statins (i.e. fluvastatin, simvastatin) may further support the use of this drug in HIV patients. The main limitation is the cost, a consideration that should encourage prescription of this drug only when more physiological measures, such as diet and exercise, have been tested in advance.

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New Insights on Rilpivirine Resistance

Nonnucleoside reverse transcriptase inhibitors (NNRTI) are popular components of combination antiretroviral therapy. Until 2006, the NNRTI family had only two drugs in Europe (efavirenz and nevirapine) and another (delavirdine) in North America. Despite their proven efficacy, the clinical use of first-generation NNRTI has been limited by side effects, low barrier to resistance, and broad cross-resistance. To try to overcome these limitations, several second-generation NNRTI have been developed. Etravirine was approved in 2007; it is active against a broad spectrum of wild-type and first-generation NNRTI-resistant HIV-1 viruses. In May 2011, the FDA approved rilpivirine (TMC-278), another second-generation NNRTI, based on the 48-week results of the phase III ECHO and THRIVE clinical trials (Molina, et al. Lancet. 2011;378:238-46; Cohen, et al. Lancet. 2011;378:229-37). More importantly, in August 2011, the FDA approved Complera™, a fixed co-formulation of emtricitabine/tenofovir/rilpivirine (200/300/25 mg).

The ECHO and THRIVE trials showed that rilpivirine was non-inferior to efavirenz in terms of efficacy at 48 weeks when given along with a two-nucleos(t)ide backbone. Patients treated with either rilpivirine or efavirenz experienced high virologic response rates (83 and 86% for rilpivirine compared with 83 and 82% for efavirenz in ECHO and THRIVE, respectively). Moreover, mean CD4 counts continuously increased from baseline in both groups. The proportion of patients with virologic failure was low in the pooled 48-week analysis, but higher among rilpivirine- than efavirenz-treated subjects (10%; 72/686 vs. 6%; 39/682). Moreover, more rilpivirine-treated subjects with plasma HIV RNA > 10^5 copies/ml at the start of therapy experienced virologic failure compared to subjects with < 10^5 copies/ml (17 vs. 5% for rilpivirine compared to 7 vs. 5% for efavirenz).

Mutation E138K was the most frequent change selected in patients who failed therapy with rilpivirine (45%) in the ECHO and THRIVE trials. This change was generally seen along with M184I (34%), which confers lamivudine and emtricitabine resistance (Rimsky, et al. Antivir Ther. 2011;16(Suppl 1):A17). The high prevalence of E138K/M184I instead of E138K/M184V cannot be explained by differences in levels of drug resistance. In fact, the combination E138K/M184I does not confer higher levels of resistance to rilpivirine and lamivudine, compared to the double mutant E138K/M184V (Xu, et al. J Virol. 2011; in press). To understand why selection of M184I is favored over M184V in patients failing on rilpivirine,

drug susceptibility, infectivity, relative fitness and reverse transcriptase (RT) activity of HIV-1 carrying E138K/M184I or E138K/M184V was evaluated. A greater relative fitness and virion-associated RT activity in the presence of E138K/M184I was seen. Indeed, the presence of M184I/V restored the impaired replication capacity of E138K mutants. Likewise, it ameliorated the reduced RT processivity at low deoxynucleoside triphosphate (dNTP) concentrations. At this time, it is unclear whether E138K or M184I emerges first, and further longitudinal examinations of patients on rilpivirine are warranted.

Drug resistance interpretation systems for antiretroviral agents (Stanford, ANRS, etc.) have recently incorporated predictions of virologic response to rilpivirine based on the available information derived from the ECHO and THRIVE trials, *in vitro* studies, and expert opinion. The Drug Resistance Platform of the Spanish AIDS Research Network (www.retic-ris.net) has weighted NNRTI resistance associated mutations. For rilpivirine resistance, at least two mutations at the RT have to be present. Those with the greatest impact are at four codons (K101E/P/T, E138A/G/K/R, Y181C/I/V, M230L), while changes at another nine positions display a lower impact (V90I, L100I, V106A/I, V108I, V179F/I/L, Y188I, G190E, H221Y, F227C/L). However, in the presence of M184I, only one mutation (E138K or K101E) is enough to result in high-level resistance to rilpivirine. This information is important for clinicians, particularly when rescue of patients failing on nevirapine or efavirenz is being considered. On the other hand, it is intriguing why virologic failures seem to be less frequent with efavirenz than rilpivirine, as the former displays a lower barrier to resistance.

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HIV Guidelines

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U.S. Department of Health and Human Services. Panel on Guidelines for Adults and Adolescents. Updated Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. January 10, 2011. http://aidsinfo.nih.gov/

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Hirsch M, Günthard H, Schapiro J, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International AIDS Society-USA panel.
Clin Infect Dis. 2008;47:266-85.

Soriano V, Puoti M, Sulkowski M, et al. Care of patients coinfected with HIV and hepatitis C virus: 2007 updated recommendations from the HCV-HIV International Panel.
AIDS. 2007;21:1073-89.

HIV Conferences

13th European AIDS Conference (EACS)
Belgrade, Serbia. October 12-15, 2011
www.eacs-conference2011.com

19th Conference on Retroviruses and Opportunistic Infections (CROI)
Seattle, WA. March 5-8, 2012
www.retroconference.org

International Symposium of HIV & Emerging Infectious Diseases (ISHEID)
Marseille, France. May 23-25, 2012
www.isheid.com

8th HIV & Hepatitis Co-Infection Workshop
Madrid, Spain. May 30-June 1, 2012
www.virology-education.com