Hot News

Efficacy of Tipranavir for Multidrug-Resistant HIV Infection

Tipranavir may be helpful for multidrug-resistant HIV infection according to the interim results of the RESIST studies, two open-label trials recently reported in the literature (Gathe, et al. CID 2006;43:1337-46; Cahn, et al. CID 2006;43:1347-56). Both RESIST-1 and RESIST-2 showed that ritonavir-boosted tipranavir (TPV/r) had greater antiviral activity at week 24 than did other comparator ritonavir-boosted protease inhibitors (CPI/r) in treatment-experienced patients.

RESIST-1 enrolled 620 antiretroviral-experienced patients at 125 sites in the USA and Australia. Before randomization, all patients had genotypic resistance testing that was used to select a CPI/r and an optimal background regimen. Patients were then randomized to be treated with TPV/r or CPI/r, and were stratified based on pre-selected PI and enfuvirtide use. At baseline, the mean plasma HIV-RNA was 4.7 $\log_{10}$ copies/ml and the mean CD4+ count was 164 cells/mm^3. At week 24, 42% of patients in the TPV/r group and 22% of those in the CPI/r group had reductions in plasma viremia ≥ 1 $\log_{10}$ copies/ml (intent-to-treat analysis; $p < 0.0001$). The mean CD4+ gains were 54 cells/mm^3 in the TPV/r group and 24 cells/mm^3 in the CPI/r group.

Using a similar design, RESIST-2 randomized 863 patients at 171 sites in Europe and Latin America. The mean baseline plasma HIV-RNA was 4.7 $\log_{10}$ copies/ml and the mean baseline CD4+ count was 218 cells/mm^3. Preplanned 24-week efficacy analyses of 539 patients showed treatment response rates of 41% with TPV/r and 15% with CPI/r (intent-to-treat analysis; $p < 0.0001$). The mean CD4+ gains were 51 cells/mm^3 in the TPV/r group and 18 cells/mm^3 in the CPI/r group.

These results establish the superior antiviral activity of TPV/r plus an optimized background regimen compared with a CPI/r regimen. Furthermore, the safety profile of TPV/r was comparable with that of other ritonavir-boosted PI, although overall liver-enzyme elevations and lipid abnormalities tend to be more common with TPV/r. In clinical practice, TPV/r may offer the opportunity of therapeutic success to patients with drug-resistant HIV strains. The 48-week data for the combined populations of RESIST-1 and RESIST-2 have just been released in a separate manuscript (Hicks, et al. Lancet 2006;368:466-75) and the message is largely the same, confirming that tipranavir can be an important component of effective treatment in HIV patients with highly resistant infections. Of note, the best outcomes were achieved when the drug was given with at least one additional active agent. Moreover, when good responses were achieved earlier, they lasted longer. This is in agreement with the recent reinforcement of the importance of achieving undetectable viremia (< 50 HIV-RNA copies/ml) and not just some degree of partial viral suppression in the setting of salvage therapy. The durable benefit which follows this goal requires, in most cases, the prescription of at least two active agents in the rescue regimen. The RESIST studies have shown that tipranavir should be considered as one of these salvage drugs.

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HIV Intersubtype Recombination: Discordance and Harmony of *In Vitro* Experiments and Observations from Sequence Analysis of Circulating Recombinants

Recombination has been identified to influence the rate and paths of evolution in many species. Retroviral recombination was initially identified in avian tumor viruses (Vogt P, Virology 1971;46:947-52), while the impact of recombination on the evolution of HIV-1 has been documented recently, showing that at least 20% of the circulating strains are intersubtype recombinants (Peeters M, Aids 2000; 14:S129-40). Homologous recombination in HIV-1 can be differentiated at three levels: between strains of the same subtype (intrasubtype), different subtypes (intersubtype) and between strains of different groups (intergroup).

On the other hand, two different models have been proposed for the mechanism of retroviral recombination, each describing the procedure of the strand transfer during synthesis of minus (–) DNA strand (Vogt P, Virology 1971;46:947-52; Coffin J, J Gen Virol 1979;42:1-26) or plus (+) DNA strand (Boone L, J Virol 1981;37:117-26; Boone L, J Virol 1981;37:109-16; Junghans R, Cell 1982;30:53-62). A series of experiments have been implemented in order to clarify the mechanistic features of recombination in HIV and other retroviruses, most of which involved strains of close similarity (same subtype) (Yu H, J Biol Chem 1998;273:28384-91; Zhang J, Science 1993;259:234-8; Zhang J, J Virol 2000;74:2313-22; Quinones-Mateu M, J Virol 2002; 76:9600-13).

Recently, a paper of Baird, et al. (Baird H, Nucleic Acids Res 2006;34:5203-16) describes the find-

ings from an *in vitro* study of HIV-1 intersubtype recombination in the C1-C4 region of the gp120 gene. Mainly, their aim in the study was to determine the sequence characteristics related to the location of the recombination breakpoints after single and multiple infection cycles using isolates of subtypes A and D. Firstly, Baird, et al. conclude that the distribution of the breakpoints is not random, indicating the existence of certain hotspots. Moreover, they found that homopolymer stretches play a significant role in promoting template switching, while they failed to identify any significant correlation of the A/U content of the breakpoint region and the frequency of recombination. On the other hand, they found that sequence similarity at the breakpoint as well as in the region downstream (with respect to the + strand) of the breakpoint is related to the observed distribution of the breakpoints. Finally, they calculated that the frequency of the experimental recombination in-between more divergent isolates (different subtype) is lower than the one observed in-between closely related isolates (same subtype), reinforcing the significance of the sequence similarity's contribution in promoting the mechanism of recombination.

In our paper on the analyses of 34 intersubtype HIV-1 globally circulating recombinants (Magiorkinis G, J Gen Virol 2003;84:2715-22), we suggested that the polarity of the newly observed similarity/breakpoint correlation is a vector, the resultant of which shows the direction of the DNA synthesis for the majority of the recombination events. According to this hypothesis, and considering the fact that the similarity at each breakpoint was higher upstream of intersubtype recombination hotspots (with respect to the + strand), recombination events should have occurred during synthesis of the plus (+) DNA strand, in contrast to what was evidenced by the previous *in vitro* experiments.

Comparing these two approaches, the common finding is that the distribution of the breakpoints differs significantly from the uniform, and since this happens, there should be some sequence characteristics affecting the disturbance of the uniform-random hypothesis. The hypothesis that the similarity of the sequence should affect the distribution, and especially in the region upstream of the breakpoint with respect to the direction of reverse transcription, is confirmed by the new findings. However Baird, et al. found a higher sequence similarity downstream from the breakpoint (with respect to the (+) strand, meaning upstream with respect to the (–) strand), while Magiorkinis, et al. detected the peak of similarity/breakpoint correlation upstream with respect to the (+) strand. Whether this discordance results from a difference between the *in vitro* and *in vivo* isolates, or supports two complementary mechanisms, the first (Baird, et al.) lying in the micromolecular level and the second (Magiorkinis, et al.) in the macromolecular level, still remains a problematic question.

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Nevirapine-Associated Hepatotoxicity in Virologically Suppressed Patients – Role of Gender and CD4+ Cell Counts

The US Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA) have issued a warning in the nevirapine package-insert recommending not initiating nevirapine in adult women with CD4+ lymphocyte counts > 250 cells/mm^3 or in adult men with a count > 400 cells/mm^3 because of a higher risk of hepatotoxicity. The data was mainly derived from a retrospective analysis of the Boehringer Ingelheim databases, including almost exclusively antiretroviral-naive patients. Due to its low price, lack of influence on lipid and glucose metabolism, and safety for pregnant women and newborns, nevirapine has been widely used in both the developed and developing world. Nevirapine has also been frequently prescribed in simplification of protease inhibitor-containing therapies, and the risk of major toxicities in this setting seems to be lower than in drug-naive patients.

A recent meta-analysis of published, randomized studies assessing the risk of hepatotoxicity when stable and virologically suppressed patients were switched to a nevirapine-containing antiretroviral therapy, stratifying by gender and CD4+ lymphocyte count, was presented orally last September at the 46th ICAAC 2006 (San Francisco). The following clinical trials were reviewed: i) NEFA, a randomized, multicenter study which analyzed the safety of the substitution in HIV-1 virologically suppressed patients treated with protease inhibitors to nevirapine, efavirenz or abacavir; ii) PREVINHE II, the GESIDA (Grupo de Estudio del SIDA) 26/02 study, a double-blind, placebo-controlled trial conducted to asses the impact of cetirizine (Zyrtec®) to prevent nevirapine-associated rash; iii) QDLLuita, a randomized, multicenter study to evaluate an antiretroviral treatment simplification with nevirapine in protease inhibitor-experienced patients with HIV-associated lipodystrophy; and iv) Study 1100.138, a randomized, international study sponsored by Boehringer Ingelheim which examined the effects of a short course of prednisone on the incidence of rash associated with nevirapine in HIV-1 patients.

A pooled total of 410 patients were analyzed in the meta-analysis. No statistical differences were

observed between low CD4+ groups (women < 250, men < 400 cells/mm^3) and high CD4+ groups (women > 250, men > 400 cells/mm^3) in terms of age, sex, CD4+ nadir count, previous AIDS-defining events, risk group, and hepatitis C or B coinfection, except for baseline abnormal ALT/AST serum levels that were more frequent in the low CD4+ group (Chi-squared test; p = 0.014).

During the first three months of nevirapine-containing therapy, three patients (2%) in the low CD4+ and 12 patients (4%) in the high CD4+ groups developed hepatotoxicity, and 17 patients (13%) in the low CD4+ and 28 (10%) in the high CD4+ groups had a rash. No patients in the low CD4+ and two (1%) in the high CD4+ groups developed symptomatic hepatitis. No patients died. Using a meta-regression model, none of the following variables showed a statistically significant association with an increased risk of hepatotoxicity or death at three months: baseline CD4+, gender, hepatitis C coinfection, or age. The risk of hepatotoxicity or death at any moment during the evolution was similar in both groups, with a combined HR of 0.77 (95% CI: 0.30-1.99; p = 0.646). Analysis of the risk of hepatotoxicity or rash or death among groups obtained similar results (combined HR of 0.99 [95% CI: 0.61-1.60; p = 0.964]).

These results suggest that being male with ≥ 400 cells/mm^3 or female with ≥ 250 cells/mm^3 when starting a nevirapine-containing antiretroviral therapy as simplification or maintenance therapy in virologically suppressed patients is not associated with an increase risk of developing hepatotoxicity, rash or death, compared to drug-naive patients.

At the XVI AIDS 2006 Conference (Toronto), Mocroft, et al. presented the results of the EuroSIDA cohort, assessing the risk of discontinuation of nevirapine due to toxicity in antiretroviral-experienced patients. From the database of EuroSIDA, they identified 1484 patients who had started a nevirapine-containing antiretroviral therapy. In accordance with the results of the meta-analysis, they found that unlike naive patients, the antiretroviral-experienced ones starting nevirapine-containing therapy (irrespectively of having high or low CD4+ counts) had a similar risk of discontinuation due to toxicities (hepatotoxicity and others) or patient/physician choice.

Moreover, similar results have been obtained from a cohort study in Munich, Germany. They included 507 patients who received nevirapine with a follow-up of 817 patient-years. Using a multivariate analysis, the coinfection with hepatitis B or C and elevation of transaminases at baseline were selected as independently associated with high risk of hepatotoxicity but not gender, CD4+ cell count, or being antiretroviral naive or experienced.

In summary, the combined results of these three studies suggest that virologically suppressed patients switching to nevirapine as a part of a simplification regimen do not show a higher risk of hepatotoxicity or rash, independent of gender or CD4+ cell counts.

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