Continuing Benefit from Antiretroviral Therapy

Strategies for continuing benefit from antiretroviral therapy were discussed at the Chicago meeting by Thomas C. Merigan, Jr, MD, from the Stanford University School of Medicine, Stanford, California.

According to Dr Merigan, such factors as genotypic resistance to antiretroviral agents, presence of SI vs NSI variants, and viral burden must be taken into account in accurately determining patient response to treatment and guiding ongoing therapy. His presentation focused on recent investigations of development of antiretroviral resistance and the relationship of genotypic resistance to disease progression.

Genotypic resistance in monotherapy

Using a double-nested PCR technique to detect the HIV RT codon 215 mutation conferring zidovudine resistance in patients from ACTG 019 and ACTG 016 who were treated at their institution, Dr Merigan and colleagues initially found that patients with virus exhibiting this mutation had experienced a 50% decline in CD4+ cell count over the course of 3 years, whereas counts had remained stable in those with wild type virus, and that appearance of the mutation preceded decline in CD4+ cell count by several months. It was also determined that the appearance of mutant strains in serum preceded PCR quantitated increase in viral burden, with viral load in patients with wildtype virus in PBMCs and mutant virus in serum being comparable to that in patients with wildtype virus in both PBMCs and serum and a marked increase in viral load being observed when mutant virus was present in both PBMCs and serum.

A subsequent investigation assessing the impact of presence of the codon 215 mutation and SI strains in zidovudine-treated patients showed that each was a significant independent predictor of both CD4+ cell count decline and increase in viral burden (Table 2). For the next three years, patients with neither viral characteristic exhibited a slight increase in CD4+ cell count and those with both characteristics had the greatest viral load and the greatest decline in CD4+ cell count. Dr Merigan stated that whereas resistance genotype can now be readily assessed via PCR, determination of SI vs NSI phenotype via culture still requires several weeks; he suggested that investigation of the viral envelope changes associated with the SI property might ultimately lead to a more rapid molecular biologic identification technique.

Dr Merigan also presented data from 70 patients showing that the didanosine resistance mutation at codon 74 was present in mixed form in 10% of patients within 8 weeks after switching from zidovudine to didanosine treatment, with the proportion of patients exhibiting either a mixed population or all mutant virus increasing to nearly 60% by 24 weeks. More than 85% of these patients had a codon 215 mutation at the time of the switch to didanosine; during didanosine therapy, virus in 28% of those with this mutation reverted to wild-type codon 215 within 24 weeks. Analysis of CD4+ cell count trajectory during 24 weeks of didanosine treatment showed that appearance of the codon 74 mutation was associated with a precipitous decline; analysis of viral burden by quantitation of serum HIV RNA showed that patients developing the mutation had a 2.69-fold increase compared with a 1.66-fold increase in those without the mutation.

Genotypic resistance in combination therapy

Patterns of genotypic resistance are more complicated in the setting of combination therapy. In ACTG 143, asymptomatic patients with CD4+ cell counts of 200 to 500/μL, half of whom had received <12 months prior zidovudine therapy and half of whom had received no prior antiretroviral therapy, received either didanosine alone or a didanosine-zidovudine combination. Resistance traits in didanosine monotherapy recipients were limited to the RT codon 74 mutation. In some patients, combination therapy was associated with the development of the same zidovudine resistance mutations associated with zidovudine monotherapy – ie, at codons 215, 70, 41, 67, and 219, with the codon 74 mutation being seen in only a small proportion during the first year of treatment. However, six combination therapy patients followed for up to 2 years developed mutations at codons 151, 62, 75, 77, and 116; isolates with these mutations were resistant to both didanosine and zidovudine despite the absence of the codon 74 and 215 mutations and exhibited decreased susceptibility to zalcitabine and stavudine (d4T), agents not previously encountered by the patients.

According to Dr Merigan, it appears that these multidrug resistance mutations result from the selective pressure on the virus to avoid development of concomitant codon 74 and codon 215 mutations, which has been associated with reversion to susceptibility to zidovudine; Dr Merigan noted that a compensatory reduction in zidovudine resistance for virus with the codon 215 mutation has also been observed with concomitant mutations conferring resistance to NNRTIs or to the nucleoside analogue 3TC. Measurement of viral burden (plasma HIV RNA) over 2 years in the combination-therapy patients showed that it generally was maintained after an initial drop in patients with drug-susceptible and culture-negative strains, whereas increases were generally observed in patients with zidovudine-resistant, multidrug-resistant, or SI strains. According to Dr Merigan, the time of increase in patients with the multidrug resistant strains has correlated with the appearance of the codon 151 mutation in mixed form, with full-blown failure of drug treatment occurring once the mutant form has become the predominant species. Dr Merigan also presented data from these patients indicating that although an increase in viral load measured as HIV RNA in plasma corresponded with decline in CD4+ cell count, it did not necessarily occur prior to cell count decline.

Monitoring genotypic resistance and SI vs NSI phenotype in clinical trials

In summarizing these data, Dr Merigan stressed that the behavior of virus in response to treatment must be known to guide further treatment, citing develop-

continued on page 16

Table 2. CD4+ Cell Count Change and Viral Burden According to Proviral DNA Codon 215 Genotype and SI vs NSI Phenotype in Patients Receiving Zidovudine

	Wildtype 215 NSI	*Wildtype 215 SI*	*Mutant 215 NSI*	*Mutant 215 SI*
No. of patients	10	6	10	6
CD4+ cell count change (cells/μL)	+28	–66	–160	–252
% CD4+ cell count change	+10%	–16%	–41%	–54%
HIV copies/10^6 CD4+ cells	467	1380	2510	21,480
HIV RNA copies/mL plasma	43,650	60,230	100,460	210,000

Upcoming Events from Yokohama*

The UCLA AIDS Institute is sponsoring a clinical research symposium, Treatment of HIV Disease: Advances and Future Challenges. In Yokohama, August 12. The symposium will be broadcast live by satellite to 10 US sites (Aug. 11). Registration required for admission to the symposium or satellite sites. Contact: Call 800-535-1307 for site information, registration or copies of proceeedings. Educational grant support: Roche Laboratories.

Live interactive videoconferences from Yokohama presenting community and medical updates will be broadcast to US sites on Aug. 9 and 11. Contact: World Health Communications at 800-433-4584 (or 800 521-1177 in New York State) for site information and registration. Educational support: Burroughs Wellcome Co.

*These programs are not affiliated with IAS-USA

Continuing Benefit *continued from page 6*

ment of specific resistance and the presence of SI strains as the two major pathways by which failure of treatment currently occurs. He maintained that resistance markers and viral load quantitation will become increasingly important in performance of drug trials. In this regard, he described the recently initiated ACTG 244, in which patients with CD4+ cell counts of 300 to 600/μL who have received zidovudine for less than 2 years and in whom viral DNA and RNA is free of the codon 215 mutation will be followed for development of the mutation. At the time that mutation is observed, patients will be randomized to receive didanosine plus zidovudine, didanosine plus zidovudine plus the NNRTI nevirapine, or continued zidovudine. CD4+ cell count, viremia, HIV proviral load, SI vs NSI phenotype, and codon 215 mutation status will be followed to determine if immunologic and virologic deterioration can be blocked by early detection of the mutation and early alteration of therapy. He stated that virologic information also is to be used in a phase I/II study of the protease inhibitor Ro31-8959 to be conducted at his institution. Assessment in this trial will include identification of the HIV protease codon 48 and 90 mutations associated with protease inhibitor resistance, identification of phenotypic resistance, and PCR quantitation of plasma HIV RNA. According to Dr Merigan, after the initial 24 weeks of study, patients will be followed and have protease inhibitor administration resumed if there is an increase in PCR quantitated viral burden. ■

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