Antiretroviral Update: Newer Investigational Drugs

Characteristics of selected new drugs from established and novel classes of antiretrovirals were discussed at the Chicago course by Roy M. Gulick, MD, MPH.

As of mid-1999, 14 antiretroviral drugs have been approved for use in treating HIV-1 infection. A large number of newer, investigational drugs representing established and novel classes are at varying stages of development (Table 1). Some of these drugs may prove to provide partial remedies to limitations of current regimen options, including problems with adverse effects and tolerability, pharmacokinetic interactions, adherence, and resistance and cross-resistance. Dr Gulick described the characteristics of selected investigational drugs from each antiretroviral class: the nucleoside reverse transcriptase inhibitor (nRTI) emtricitabine, the nucleotide reverse transcriptase inhibitor (n*t*RTI) adefovir, the nonnucleoside reverse transcriptase inhibitor (NNRTI) emivirine, the protease inhibitors amprenavir (recently approved) and lopinavir, and the fusion inhibitor pentafuside.

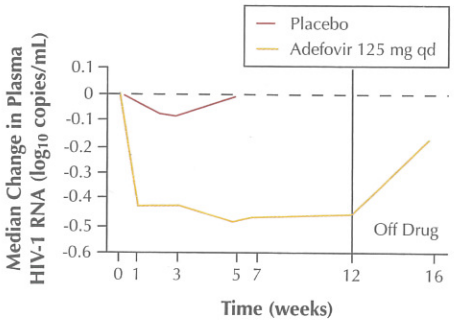

Figure 1. *Median change in plasma HIV-1 RNA level during adefovir monotherapy. Adapted from Deeks SG, et al.* J Infect Dis. *1997;176:1517–1523.*

EMTRICITABINE (FTC)

The nRTI emtricitabine (FTC) exhibits anti-HIV-1 potency in vitro 4 to 10 times greater than the related drug lamivudine and also exhibits activity against hepatitis B virus. The proposed dosage of the drug is 200 mg once a day; didanosine is the only currently-approved nRTI routinely given on a once-daily schedule. Phase III studies of emtricitabine are under way. Adverse effects have been uncommon, consisting primarily of gastrointestinal tract effects and headache. The drug is eliminated largely via renal mechanisms. Resistance in vitro is conferred by the reverse transcriptase M184V mutation associated with lamivudine resistance, indicating cross-resistance between the 2 drugs. In a Phase I dose-escalation study of emtricitabine, 200 mg once a day or twice a day exhibited a trend toward greater reduction of serum viral load, achieving maximal reductions of greater than 1.5 log. Data from a subsequent Phase II/III study indicate similar degrees of effect of once-daily dosing of 25, 100, or 200 mg emtricitabine and 150 mg twice a day of lamivudine.

ADEFOVIR DIPIVOXIL

The n*t*RTI adefovir dipivoxil is in Phase III studies and studies in antiretroviral-experienced patients and currently is available through an expanded access program. Adefovir exhibits in vitro potency against HIV-1 (90% effective dose [ED_{90}] of 0.007-7 μM), as well as against cytomegalovirus and hepatitis B virus. The proposed dosage is 60 mg once a day; there are no food restrictions with usage. The drug undergoes renal excretion. Adverse effects include gastrointestinal tract effects, carnitine depletion, and proximal renal tubular dysfunction. In vitro resistance mutations have been detected at reverse transcriptase codons 70, 69, and 65. The emergence of mutations in vivo has been uncommon to date. Figure 1 shows degree of reduction in viral load in a Phase I study with an initial formulation equivalent to the current 120 mg dose. In a virologic substudy of a Phase II study in which adefovir was added to existing regimens, it was observed that a greater decrease in plasma HIV-1 RNA level (0.94 log) occurred in patients exhibiting the M184V lamivudine-associated resistance mutation than

Table 1. Selected Investigational Antiretroviral Drugs

Class	Investigational Drugs
Nucleoside reverse transcriptase inhibitors	emtricitabine (FTC), lodenosine (FddA), BCH-10652 (dOTC), DAP/DXG
Nucleotide reverse transcriptase inhibitors	adefovir dipivoxil, PMPA
Nonnucleoside reverse transcriptase inhibitors	emivirine (MKC-422), AG1549 (S-1153), PNU-142721, DMP-961, DMP-963, GW420867X
Protease inhibitors	lopinavir (ABT-378), tipranavir, L-756, 423, BMS-232, 632, AG1776 (JE-2147), DMP-450, PD-178390
Fusion inhibitors	pentafuside (T-20), FP-21399, T-1249