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Emtricitabine
A Viewpoint by Raymond F. Schinazi

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Four classes of antiretroviral drugs are available to treat individuals infected with HIV: the nucleoside reverse transcriptase inhibitors (NRTI), the nonnucleoside reverse transcriptase inhibitors (NNRTI), the protease inhibitors (PI) and fusion inhibitors (FI). The currently accepted standard of care for HIV infection involves the use of three drugs in combination regimens. Although at times arduous, the use of combination therapy has profoundly reduced the morbidity and mortality associated with HIV infection. Unfortunately, most of the 19 approved anti-HIV drugs and the combination(s) of these drugs have significant limitations including toxicity, the selection of drug-resistant variants, pharmacokinetic interactions with other agents and poor adherence due to complex dosing regimens. These limitations have necessitated the continued search for anti-HIV agents with an improved clinical profile.

Emtricitabine (Emtriva™[1]), the 2′,3′-dideoxynucleoside analog (2R,5S)-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (FTC), is a potent and selective inhibitor of HIV and hepatitis B virus (HBV) replication *in vitro* and in the clinic. Preclinical and clinical studies conducted to date provide critical differences between emtricitabine and other nucleoside analogs currently approved for the treatment of these infections. In particular, the introduction of fluorine into the C-5 position of lamivudine confers higher affinity of the nucleotide form of emtricitabine toward the viral polymerase, resulting in generally greater *in vitro* potency and statistically significant decreased incidence in the selection of M184V mutant HIV in the clinic.

It is apparent that emtricitabine represents one of the most potent anti-HIV agents identified to date, producing an almost two $\log_{10}$ drop in viral load as monotherapy with a 200mg once-daily dose. In addition, the clinical profile of emtricitabine has demonstrated the following key features: (i) a plasma half-life of approximately 8–10 hours with linear kinetics; (ii) an intracellular emtricitabine triphosphate half-life of ≥39 hours, which supports once daily dosing; (iii) no significant drug-drug interactions which would limit the use of emtricitabine in combination therapy; (iv) comparable safety and efficacy to lamivudine; and (v) a low incidence of M184V mutations. The latter is an important finding suggesting that emtricitabine could increase the antiviral durability of oxathiolane nucleoside analog-containing drug regimens.

Although the HBV clinical development programme has entered the pivotal phase, there are already data to suggest that at the same 200mg once-daily dose selected for HIV treatment, there is a lower incidence of the rtM204V mutation than has historically been reported for lamivudine. This also suggests that emtricitabine will be an extremely important drug for the treatment of patients co-infected with HIV and HBV. In effect, Gilead Sciences has indicated that they are co-formulating tenofovir with emtricitabine. Trials comparing this combination head-to-head to with a combination of lamivudine plus zidovudine are ongoing.

Disclosure: Dr R.F. Schinazi receives royalties for the sale of lamivudine and is entitled to royalties from future sales of emtricitabine as recognition for his contribution to the discovery and development of both nucleoside analogs. ▲

1 Use of tradenames is for product identification purposes only and does not imply endorsement.