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Lopinavir

A Viewpoint by Robert L. Murphy

Department of Medicine, Northwestern University Medical School, Chicago, USA

Lopinavir is a novel HIV-1 protease inhibitor (PI) that is 10 times more potent than ritonavir. It differs from available PIs because of its exquisite sensitivity to pharmacokinetic enhancement by low doses of ritonavir, a potent inhibitor of the cytochrome P450 3A isoenzyme. In HIV-1 infected patients, the mean trough plasma concentrations were 50- to 100-fold higher than the protein binding-corrected EC_{50} value for wild-type virus. These drug levels are substantially higher than those seen with other currently available PIs, which are typically 1- to 4-fold higher than the protein binding-corrected EC_{50} values.

Lopinavir has been administered to treatment-naive and -experienced patients in phase II trials for 48 to 72 weeks with favourable results. In the treatment-naive group, a successful virologic response, defined as suppression of plasma HIV-1 RNA to <400 copies/ml, was observed in 82% of subjects at 72 weeks when lopinavir was administered with stavudine and lamivudine. In the treatment-experienced group, plasma HIV-1 RNA was suppressed below 400 copies/ml in 70% of subjects who also added nevirapine (a non-nucleoside reverse transcriptase inhibitor) and changed background nucleoside reverse transcriptase inhibitors. The CD4 cell count in these studies was robust, increasing by approximately 225 and 125 cells/μl, respectively.

The adverse event profile of lopinavir is favourable. In the above studies, only 1 patient in the naive and 3 patients in the experienced groups discontinued study medications because of a drug-related adverse event. Up to 21% of patients reported minor, generally self-limiting gastrointestinal complaints, none of which resulted in drug discontinuation. Moderate elevations in serum triglycerides and cholesterol were reported in 20% of naive and 39% of experienced patients, and were generally partially responsive to diet and anti-lipid therapies. Significant elevations in hepatic transaminase occurred in 13% of patients and were much more likely to occur in those co-infected with hepatitis B and/or C. In 1 instance, lopinavir was discontinued because of persistent hepatic transaminase elevations.

Because of its excellent antiviral activity, favourable pharmacokinetic properties and good tolerability profile, lopinavir is likely to provide a significant advantage over other antiretroviral agents when used in a 3- or 4-drug combination treatment regimen. Concern still exists for patients co-infected with viral hepatitis and those with hyperlipidaemia. Larger phase III studies are underway that will further address these issues.