Safety and antiviral activity of lopinavir/ritonavir-based therapy in human immunodeficiency virus type 1 (HIV-1) infection

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Protease inhibitor-based antiretroviral therapy has been shown to decrease the morbidity and mortality associated with human immunodeficiency virus type 1 (HIV-1) infection. However, many of the available agents in this class suffer shortcomings, including poor tolerability, difficult dosing regimens, and variable drug concentrations which may lead to generation of viral resistance. Lopinavir/ritonavir (Kaletra) has been designed specifically to address some of these shortcomings. Excellent therapeutic efficacy has been documented for lopinavir/ritonavir in multiple clinical trials in both antiretroviral-naive and -experienced patients. Development of resistance is a rare event in persons initiating therapy with lopinavir/ritonavir as their first protease inhibitor. The main side effects associated with lopinavir/ritonavir are gastrointestinal disturbances and elevations of serum lipids. Current antiretroviral therapy guidelines list lopinavir/ritonavir as the consensus first-line protease inhibitor recommended in the initial therapeutic regimen in persons infected with HIV-1.

Keywords: antiretroviral therapy, protease inhibitors, acquired immune deficiency syndrome, AIDS

Introduction

In areas where antiretroviral therapy is widely available, its impact on the morbidity and mortality associated with human immunodeficiency virus type 1 (HIV-1) infection has been striking. The HIV-1 protease inhibitors, which prevent cleavage of the gag-pol polyprotein and result in production of immature, non-infectious viral particles, are important components of current antiretroviral regimens. However, many agents in this class are limited by various factors, including poor tolerability, difficult dosing requirements, and low serum trough concentrations which may facilitate the development of resistance.

The fifth protease inhibitor to receive U.S. Food and Drug Administration (FDA) approval, lopinavir/ritonavir (Kaletra) was specifically designed to overcome some of the limitations of its predecessors. The active part of the fixed-dose combination drug, lopinavir, is metabolized via the hepatic enzymes CYP3A4 and CYP3A5, and when given alone, does not achieve drug concentrations sufficient to suppress HIV-1 replication. The second component of the combination, ritonavir, potently inhibits these hepatic enzymes in a concentration-dependent manner. The combination of lopinavir and ritonavir thus achieves significantly increased plasma levels of lopinavir, well above the mean 50% inhibitory concentration (IC₅₀) for wild-type HIV-1.

Lopinavir was designed to avoid the resistance problems which had arisen in Abbott’s first protease inhibitor, ritonavir. The development of resistance to ritonavir was often due to a mutation of the amino acid valine at position 82 in protease. Lopinavir was specifically designed to avoid interaction with the valine at this position, thus avoiding development of resistance by this mechanism.

Antiviral activity and resistance profile of lopinavir/ritonavir-based therapy

Multiple clinical trials have demonstrated the efficacy of lopinavir/ritonavir-based regimens in the treatment of both antiretroviral-naive and -experienced patients. The M97-720 study is a Phase II study of lopinavir/ritonavir in combination with stavudine and lamivudine in treatment-naive patients. This study cohort has been followed for over 6 years, longer than any other group of patients treated with lopinavir/ritonavir to date. One hundred patients were enrolled in this dose-ranging study, and after 48 weeks of follow-up, HIV-1 RNA was <400 copies/mL in 85% and <50 copies/mL in 78% by intention-to-treat analysis (missing = failure). Mean CD4 cell count increases were 229 cells/mm³. Through 312 weeks of follow-up, all the patients remaining on therapy (n = 63) sustained HIV-1 RNA <400 copies/mL, and 98% had viral loads <50 copies/mL. By intention-to-treat analysis, 63% had viral loads <400 copies/mL and 62% were <50 copies/mL. Mean CD4 cell count increases over this time period were 529 cells/mm³.

A larger Phase III study in treatment-naive patients demonstrated the superiority of lopinavir/ritonavir over another protease inhibitor, nelfinavir. The M98-863 study randomized 653 adults to...
either lopinavir/ritonavir or nelfinavir, in combination with stavudine and lamivudine.\textsuperscript{12} By intention-to-treat analysis after 48 weeks, 75\% of lopinavir/ritonavir-treated patients and 63\% of nelfinavir-treated patients achieved HIV-1 RNA suppression to <400 copies/mL (\(P < 0.001\)). CD4 cell gains were similar between the two groups (207 cells/mm\(^3\) for lopinavir/ritonavir, 195 cells/mm\(^3\) for nelfinavir). Through 96 weeks of follow-up, 79\% of lopinavir/ritonavir-treated patients remaining on the study medications and 56\% of nelfinavir-treated patients maintained HIV-1 RNA <400 copies/mL.\textsuperscript{13, 13}

In treatment-experienced patients, lopinavir/ritonavir has also proven to be a valuable agent. The M97-765 study placed patients failing an initial protease inhibitor-based regimen (\(n = 70\)) on a regimen of lopinavir/ritonavir, nevirapine and nucleoside reverse transcriptase inhibitors.\textsuperscript{14} By intention-to-treat analysis after 48 weeks of therapy, 70\% of patients had HIV-1 RNA <400 copies/mL, 60\% <50 copies/mL.

Similar results were obtained in the M98-888 study which randomized single protease inhibitor-experienced patients (\(n = 288\)) to a new regimen of lopinavir/ritonavir or an investigator-selected alternative protease inhibitor, plus nevirapine and nucleoside reverse transcriptase inhibitors.\textsuperscript{15} Fifty-seven percent of patients receiving lopinavir/ritonavir had HIV-1 RNA <400 copies/mL after 48 weeks by intention-to-treat analysis, compared with 33\% receiving investigator-selected alternative protease inhibitors (\(P < 0.001\)).

Finally, study M98-957 documented efficacy of lopinavir/ritonavir in patients who had previously received two or more different protease inhibitors.\textsuperscript{16} The 57 patients in this study received lopinavir/ritonavir as well as efavirenz and nucleoside reverse transcriptase inhibitors. After 48 weeks of therapy, 65\% of patients maintained HIV-1 RNA <400 copies/mL, and 56\% <50 copies/mL by intention-to-treat analysis. Thus, the value of lopinavir/ritonavir has been demonstrated in a broad spectrum of patient types, affirming its benefit in both antiretroviral-naive and -experienced patients.

In an effort to simplify treatment regimens for patients, once-daily dosing of antiretroviral agents including lopinavir/ritonavir has been the subject of increasing numbers of studies. The M02-418 study randomized 190 antiretroviral-naive patients to either once-daily or twice-daily lopinavir/ritonavir in combination with emtricitabine and tenofovir DF.\textsuperscript{17} By intention-to-treat analysis after 48 weeks, 70\% of patients receiving once-daily therapy achieved HIV-1 RNA <50 copies/mL compared with 64\% of patients receiving twice-daily dosing. Similar results were seen in an earlier pilot study by Eron et al.,\textsuperscript{18} which randomized antiretroviral-naive patients to once- or twice-daily lopinavir/ritonavir in combination with stavudine and lamivudine.

Lopinavir/ritonavir has also been studied in a paediatric population composed of antiretroviral-naive and -experienced patients. Excellent therapeutic efficacy similar to adult populations has been demonstrated, and the medication appears to be well tolerated in this patient population.\textsuperscript{19}

As previously mentioned, lopinavir/ritonavir was specifically designed to overcome issues of resistance that have affected the efficacy of earlier protease inhibitors. In antiretroviral-naive patients, \textit{de novo} development of lopinavir/ritonavir resistance has not been demonstrated in large clinical trials. Extensive resistance testing has been completed in patients remaining on therapy after 5 years in the M97-720 study, the cohort followed for the longest time period to date.\textsuperscript{20} All patients with HIV-1 RNA >500 copies/mL at any time after week 24 had samples submitted for genotypic testing. Thirty-four patients were tested from 27 patients, and resistance testing was successfully accomplished in 22 samples from 17 patients. (Testing failed for the other specimens due to low levels of HIV-1 RNA.) No specimen demonstrated mutations in the protease gene associated with resistance to lopinavir/ritonavir. Resistance to other components of the patient’s regimen was also rare, with no patient developing mutations associated with stavudine resistance, and only 3/17 patients showing resistance to lamivudine.

A similar analysis was performed in the M98-863 study, which randomized antiretroviral-naive patients to either lopinavir/ritonavir or nelfinavir. Among patients with at least one HIV-1 RNA >400 copies/mL while receiving lopinavir/ritonavir (\(n = 51\)), no genotypic evidence of resistance in protease was demonstrated.\textsuperscript{21} This contrasted with patients receiving nelfinavir (\(n = 96\)), where 45\% of samples demonstrated a primary resistance mutation to nelfinavir, D30N or L90M (\(P < 0.001\)). Resistance to other components of the treatment regimen was also more common among patients receiving nelfinavir. Eighty-two percent of the available isolates demonstrated resistance to lamivudine in nelfinavir-treated patients, compared with 37\% of patients receiving lopinavir/ritonavir (\(P < 0.001\)). Resistance to stavudine was not observed in lopinavir/ritonavir-treated patients, and was found in 9\% of nelfinavir-treated patients.

In the M02-418 study which compared once- and twice-daily dosing of lopinavir/ritonavir, similar results were obtained. Samples from 11 patients with HIV-1 RNA >500 copies/mL between weeks 12 and 48 were available for genotypic testing. Testing was unable to be performed in three specimens due to low viral load. Of the eight specimens with genotypic results available, no resistance mutations in protease were observed.\textsuperscript{22}

### Safety of lopinavir/ritonavir-based therapy

These clinical trials have allowed the side effect profile of lopinavir/ritonavir to be well characterized. The most frequently reported adverse events are gastrointestinal, particularly diarrhoea. The most commonly noted laboratory abnormalities are elevations in lipid profiles and, less commonly, hepatic transaminases. Overall, lopinavir/ritonavir is relatively well tolerated, with low reported rates of drug discontinuation due to side effects in clinical trials.

In antiretroviral-naive patients, the most common adverse effects associated with lopinavir/ritonavir are diarrhoea, nausea and abnormal stools.\textsuperscript{9, 10, 12} Discontinuation rates as a result of adverse events were 2\% or less in these two trials. In the longest study of lopinavir/ritonavir to date, 28\% of patients reported diarrhea of at least moderate severity at some time through week 312.\textsuperscript{11} In the study comparing once- and twice-daily dosing of lopinavir/ritonavir, the incidence of diarrhoea was increased among patients receiving once-daily dosing.\textsuperscript{17} Similar adverse event profiles have been seen in antiretroviral-experienced patients, with diarrhoea being the most frequently reported adverse event of moderate or greater severity.\textsuperscript{14–16}

As a class, protease inhibitors have been associated with the metabolic syndrome, due to the association of protease inhibitor therapy with the development of hyperlipidaemia, fat redistribution and insulin resistance.\textsuperscript{23} Frank diabetes mellitus is uncommon.\textsuperscript{24} Lopinavir/ritonavir has been shown to be independently associated with the development of the metabolic syndrome.\textsuperscript{25}
Lipid elevations are the most common laboratory abnormalities associated with lopinavir/ritonavir treatment. In registrational trials, grade III/IV elevations in total cholesterol and triglycerides were reported in ~10% of antiretroviral-naive patients during the first 48 weeks of therapy. Mean increases in total cholesterol were 49–53 mg/dL and in triglycerides 111–125 mg/dL. In antiretroviral-naive patients receiving lopinavir/ritonavir for over 6 years, 23% developed grade III/IV elevations in total cholesterol, and 26% in triglycerides. Similar results were seen in protease inhibitor-experienced patients. In both patient populations, subjects with elevations at baseline were more likely to experience grade III/IV elevations during the course of the study.

While the trials mentioned above involved samples that may not have been obtained in the fasting state, some studies have been specifically designed to assess lipids measured under fasting conditions. Martinez et al. examined the impact of 6 months of lopinavir/ritonavir therapy on metabolic parameters in 353 HIV-infected patients, the majority of whom had received therapy with other protease inhibitors previously. During the follow-up period, significant increases in triglyceride levels and total cholesterol were observed. Elevated total cholesterol and triglycerides before study entry as well as the use of lipid-lowering medications at baseline were independently associated with the results. Similar results were seen in a cohort of antiretroviral-naive patients. All available data indicate that increases in lipid profiles tend to occur within the initial months of therapy, and reach a plateau thereafter.

In one study of antiretroviral-naive patients, lipodystrophy was reported in 13% of patients through week 312. This side effect (which remains relatively poorly characterized) has not been rigorously studied in other clinical trials, mainly because this complication was not widely recognized at the time the studies were designed.

Although protease inhibitors have been associated with the development of insulin resistance, significant increases in fasting glucose levels have not been reported in patients treated with lopinavir/ritonavir.

Asymptomatic elevations in hepatic transaminases have also been noted in persons treated with lopinavir/ritonavir. Grade III/IV elevations have been reported in 5–8% of antiretroviral-naive patients receiving lopinavir/ritonavir in the first year of therapy, and in 11% of patients over 6 years of therapy. Similar results were observed in antiretroviral-experienced patients. Over time, these elevations tended to normalize, and few patients discontinued therapy due to hepatic inflammation. Patients with transaminase elevations at baseline are more likely to experience elevations while receiving therapy with lopinavir/ritonavir. Concomitant infection with hepatitis B or C also appears to increase the risk of transaminase elevation, but does not increase the risk of hepatotoxicity.

Conclusions

Since its release in 2000, lopinavir/ritonavir has been an important addition to antiretroviral therapy for patients infected with HIV-1. Its potent antiretroviral activity, generally good tolerability, and high genetic barrier to resistance have made it the preferred protease inhibitor to be used as part of an initial antiretroviral regimen for adults and children. As time has passed since its release, an evolution in antiretroviral therapy has stressed simplicity in dosing with more drugs being used as once-daily therapy. In line with this trend, the FDA approved once-daily lopinavir/ritonavir therapy for use in antiretroviral-naive patients on 29 April 2005, based on the results of the two previously cited studies. This option will further simplify lopinavir/ritonavir-based treatment regimens for patients infected with HIV-1. In addition, Abbott has recently filed a supplemental New Drug Application for a new formulation of lopinavir/ritonavir which will decrease the pill burden from a total of six pills per day to four pills per day.

The dramatic success of antiretroviral therapy has forced HIV practitioners to focus on the longer-term consequences of HIV management strategies. In particular, evidence from studies of long-term antiretroviral therapy suggest that there may be an increased risk of cardiovascular disease among HIV-infected patients receiving antiretroviral therapy. This increased risk may be mediated in part by changes in lipids, and observed elevations in total cholesterol and triglycerides necessitating institution of lipid-lowering therapy remain a concern with lopinavir/ritonavir therapy. Further studies will be needed to document the causality of this association, and to determine the optimal management of HIV-infected patients with cardiovascular risk factors. The recent availability of protease inhibitors with diminished lipid effects over time may ultimately affect which drugs are preferred for initial therapy, but this remains to be determined. The observed efficacy of lopinavir/ritonavir-based therapy in a variety of settings has established the important role of this drug in the management of persons infected with HIV-1, and its continued use as a key protease inhibitor seems assured for the foreseeable future.

References

