Long-term (4 years) efficacy of lopinavir/ritonavir monotherapy for maintenance of HIV suppression

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Objectives: Data are scarce on the long-term efficacy of lopinavir/ritonavir monotherapy for the maintenance of HIV suppression. Four years of results of patients randomized to monotherapy in the Only Kaletra (OK) pilot clinical trial are presented.

Patients and methods: Twenty-one HIV-infected patients with suppressed HIV replication (<50 copies/mL) for at least 6 months and without previous failure while receiving a protease inhibitor-based regimen started lopinavir/ritonavir monotherapy. Follow-up was performed within the OK pilot clinical trial during the first 2 years and according to routine clinical practice during the 3rd and 4th years.

Results: Fourteen patients (67%) remain on monotherapy and with RNA <50 copies/mL (intention-to-treat analysis, with missing patients scored as failures). Five patients (24%) had virological rebound and all of them were successfully re-suppressed by adding two nucleosides. No major protease inhibitor mutations were found.

Conclusions: Our data support the long-term efficacy and safety of lopinavir/ritonavir monotherapy for the maintenance of HIV suppression, a finding that must be confirmed in larger studies.

Keywords: simplification, boosted protease inhibitors, antiretroviral therapy

Introduction

A number of studies have evaluated monotherapy with lopinavir/ritonavir either as initial therapy,1,2 as maintenance therapy after induction with three drugs3 or as simplification therapy in virologically suppressed patients.4–6 In terms of virological efficacy, the best results have been obtained in the three clinical trials which have used monotherapy with lopinavir/ritonavir as simplification therapy after at least 6 months of suppressed viral replication while receiving triple therapy.4–6 An important limitation of these studies is that only 2 year follow-up data are available.7,8 To completely characterize the efficacy of lopinavir/ritonavir monotherapy, longer follow-up data are required. For this reason, we communicate 4 year follow-up data on patients included in the Only Kaletra (OK) pilot clinical trial.4

Patients and methods

The OK pilot clinical trial evaluated maintenance therapy with lopinavir/ritonavir alone versus continuing lopinavir/ritonavir and two nucleosides in HIV-infected patients with suppressed HIV replication (<50 copies/mL) for at least 6 months. Details of the study design and methodology have been reported previously.4 In the OK pilot trial, patients with confirmed virological rebound (two consecutive samples with >50 HIV-RNA copies/mL) while receiving lopinavir/ritonavir monotherapy were re-intensified with baseline nucleosides if no major protease inhibitor mutations were detected in the genotype. After the end of the trial (96 weeks), all patients receiving lopinavir/ritonavir monotherapy opted to continue this treatment. These patients have been followed in our clinics according to routine clinical practice in Spain (every 3–6 months).
The study was approved by the Regional Ethics Committee for Clinical Research of the Community of Madrid and by the Spanish Agency for Medicines and Healthcare Products. All patients gave dated and written informed consent. In the present analysis, we report efficacy and safety after 4 years of follow-up.

Results

Twenty-one patients were randomized to lopinavir/ritonavir monotherapy. Seventeen (81%) patients were male. Median age was 42 years. HIV route of transmission was intravenous drug use in 8 (38%), unprotected homosexual contact in 5 (24%) and unprotected heterosexual contact in 8 (38%). Fifteen patients (71%) had had a previous AIDS diagnosis. Viral load pre-HAART was 5.11 log_{10} HIV-RNA copies/mL (median). Median time with HIV-RNA < 50 copies/mL while receiving HAART prior to monotherapy was 28.6 months. Median CD4 cell count at baseline was 662 cells/mm³, with a median nadir of 139 cells/mm³. Ten patients (48%) were co-infected with hepatitis C virus. Lopinavir/ritonavir was the first protease inhibitor for 7 patients (33%) and the second protease inhibitor for 14 patients (67%). Three patients had received prior treatment with nelfinavir, four with indinavir, five with ritonavir and two with saquinavir/ritonavir. Before randomization, the most common nucleoside combinations were zidovudine/lamivudine (33%) and stavudine/lamivudine (38%).

By intention-to-treat (ITT) (missing data include failure) analysis, 4 years after randomization, 14 patients (67%) treated with lopinavir/ritonavir monotherapy remain with virological suppression (HIV RNA < 50 copies/mL) (Figure 1).

Of the seven failures (by ITT), one was a patient who died of chronic bronchitis at week 84 while suppressed on monotherapy, and one was a patient who discontinued monotherapy while virologically suppressed and was lost to follow-up. The remaining five patients (24%) had virological rebounds during follow-up at weeks 16, 16, 24, 96 and 128. In four (80%) of these five patients, non-adherence episodes could be demonstrated using pharmacy registers for drug refills.

All five patients with virological rebound while receiving lopinavir/ritonavir monotherapy were successfully re-suppressed by adding two nucleosides. Of these five patients, four remained suppressed 51, 160, 165 and 168 weeks after re-induction. The remaining patient with virological rebound who underwent re-induction with nucleosides was lost to follow-up after re-suppression.

Genotypic resistance tests were performed in nine samples from five patients. These were four of the five patients with virological rebound while on monotherapy (one patient could not be genotyped because rebound was < 500 HIV-RNA copies/mL) and one patient who discontinued therapy during follow-up. No major protease inhibitor mutations were detected in any of the samples.

Median CD4 cell count increase after 4 years for the 14 patients receiving monotherapy was 223 cells/mm³. No discontinuations related to adverse events were observed during follow-up. One patient developed grade 3 hypercholesterolaemia. No other grade 3 or 4 clinical or laboratory adverse event was observed.

Discussion

Long-term follow-up data of our pilot trial suggest that lopinavir/ritonavir alone can maintain HIV-1 viral suppression in a large proportion of patients (67%). It is important that no patient with loss of virological suppression had development of protease inhibitor mutations. Interestingly, patients with maintenance failures were successfully re-induced by adding back prior nucleosides. At the end of the 4th year, 18 patients (86%) remain with HIV-RNA < 50 copies/mL using lopinavir/ritonavir (with or without nucleosides). As no patient has lost active drugs because of resistance development during these 4 years of follow-up, exhaustion of therapeutic options has not occurred.

Most of the virological rebounds occurred early in the trial and were probably related to suboptimal adherence in all but one patient. Irregular adherence might explain loss of virological suppression in the absence of major protease inhibitor mutation development. It has been repeatedly shown that antiretroviral-naive patients who do not adhere properly to a lopinavir/ritonavir-based regimen do not develop primary mutations in the protease gene. The rapid terminal clearance of lopinavir after a dose is missed has been proposed as the main reason for the low selective pressure of lopinavir during periods of non-adherence. It is quite remarkable that patients who required re-induction with nucleosides were able to maintain long-term virological suppression after re-induction. In our opinion, this finding argues against a negative consequence of a period of low-level viraemia in patients receiving lopinavir/ritonavir monotherapy and does not support the idea that these patients might be harbouring resistant minority species that were not detected with population genotyping.

One of the main advantages of lopinavir/ritonavir monotherapy is its lower cost, compared with triple drug therapy. Decreasing the cost of HAART is critical in low-resource

Figure 1. HIV-RNA < 50 copies/mL (ITT, MD = F): patients randomized to monotherapy in the OK trial.
settings. In developing countries, lopinavir/ritonavir monother-apy might be a useful simplification option for boosted protease inhibitor-based regimens after failure of a non-nucleoside-based first line regimen.

The most important limitation of the study is obviously its small sample size. Despite this limitation, the observed 192 week efficacy rate is encouraging. In addition, our data clearly suggest that those patients who lose viral suppression while on lopinavir/ritonavir monotherapy can be safely re-induced with prior nucleosides without any apparent loss of therapeutic options. Our data support the long-term efficacy and safety of lopinavir/ritonavir monotherapy for the maintenance of HIV suppression, a finding that must be confirmed in larger studies.

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