Monotherapy with boosted PIs as an ART simplification strategy in clinical practice

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Background: Data on the efficacy of simplifying therapy using darunavir/ritonavir and lopinavir/ritonavir monotherapy in clinical practice remain limited.

Methods: A retrospective single-centre study including patients initiating darunavir/ritonavir or lopinavir/ritonavir monotherapy with a plasma HIV-1 viral load (pVL) <50 copies/mL and at least one subsequent follow-up visit. The primary endpoint was the percentage of patients remaining free of virological failure (VF; defined as a confirmed pVL >50 copies/mL or as any change in the regimen after a single determination with a pVL >50 copies/mL) during the follow-up. We also evaluated the percentage of patients remaining free of treatment failure (TF; defined as VF or the early discontinuation of monotherapy for any reason) and compared the effectiveness of the two regimens. Effectiveness was evaluated using cumulative survival analysis (at Weeks 48 and 96). Factors associated with VF and TF were analysed using Cox regression.

Results: A total of 522 patients were included (309 receiving lopinavir/ritonavir and 213 receiving darunavir/ritonavir). The median follow-up was 64.3 (30.5–143.0) weeks. The percentage of patients free of VF and TF was 94% (95% CI 91%–96%) and 79% (95% CI 75%–82%) at 48 weeks, respectively, and 86% (95% CI 81%–89%) and 62% (95% CI 57%–67%) at 96 weeks, respectively. The risk of VF was similar for the two regimens (HR = 1.0, 95% CI 0.6–1.8; P = 0.962). Lopinavir/ritonavir monotherapy was associated with a 1.5-fold greater risk of TF (95% CI 1.1–2.1; P = 0.012) and a 2.3-fold greater risk of discontinuation of therapy due to adverse events (95% CI 1.3–3.9; P = 0.003).

Conclusions: The virological efficacy of darunavir/ritonavir and lopinavir/ritonavir monotherapy is high in clinical practice. Treatment discontinuation due to safety issues is more frequent with lopinavir/ritonavir.

Keywords: darunavir/ritonavir, lopinavir/ritonavir monotherapy, NRTI-sparing regimens, routine clinical setting

Introduction

Standard-of-care ART is based on a combination of three antiretroviral drugs including two NRTIs plus a third agent.1–3 However, since ART is lifelong and NRTIs are not exempt from toxicity, such as mitochondrial dysfunction and bone and kidney conditions,4–8 interest in NRTI-sparing regimens has grown in recent years.

Monotherapy with boosted PIs is a particularly attractive NRTI-sparing strategy in patients with suppressed viraemia. It can help to prevent NRTI-related toxicities, decrease ART-related costs and preserve future treatment options.9–11 In clinical trials, monotherapy with darunavir/ritonavir or lopinavir/ritonavir in virologically suppressed HIV-infected patients without PI-related resistance mutations has seemed to be as efficacious as triple ART for maintaining virological suppression.12–14 However, the demonstration of non-inferiority has depended on the definition of the endpoint for efficacy and on whether the NRTIs were reintroduced.12–14 Consequently, clinical guidelines for the management of HIV infection differ with respect to PI monotherapy.1–3,15 Moreover, data on the long-term efficacy and safety of this strategy in less selected populations of patients in routine clinical practice remain limited, thus indicating differences between the different boosted PIs used in monotherapy.16–19 The objectives
of this study were to explore and compare the effectiveness and safety of PI monotherapy with darunavir/ritonavir and lopinavir/ritonavir as a treatment simplification strategy in clinical practice.

Methods

We performed a retrospective single-centre study including all HIV-infected patients who initiated darunavir/ritonavir or lopinavir/ritonavir monotherapy in our clinic with a plasma HIV-1 viral load (pVL) <50 copies/mL and at least one follow-up visit. Data were retrieved from a prospectively compiled database. Only the first regimen was considered for analysis in the case of patients who had received treatment consecutively with the two monotherapies. Lopinavir/ritonavir (Kaletra\textsuperscript{\textregistered}; Abbott Laboratories, Illinois, USA) was prescribed at a dose of 400/100 mg twice daily in all cases. Darunavir/ritonavir (Prezista\textsuperscript{\textregistered}; Tibotec, Beerse, Belgium) was prescribed at 800/100 mg once daily, although some patients initially received 900/100 mg once daily until the 400 mg tablet became commercially available. The patients’ demographic and clinical characteristics were recorded when the monotherapy was started (baseline) and every 3–6 months thereafter, depending on the timing of the clinical visits. We also recorded the presence of “blips” (defined as single determinations of an HIV pVL between 50 and 400 copies/mL, with subsequent re-suppression of pVL and no changes in ART), the reasons leading to the discontinuation of treatment, adherence to treatment and the results of genotypic tests in patients experiencing virological failure (VF) when these were available. The study was approved by the Ethics Committee of Hospital Germans Trias i Pujol, Badalona, Spain and performed according to the stipulations of the Declaration of Helsinki (Seoul, 2008). All patients gave their written informed consent for their medical information to be used in scientific research.

The primary endpoint of the study was the percentage of patients remaining free of VF during the follow-up period. VF was defined as a pVL >50 copies/mL in two consecutive determinations or as any change in the monotherapy regimen after a single determination with a pVL >50 copies/mL, including the reintroduction of NRTIs. Secondary endpoints included the percentage of patients remaining free of treatment failure (TF) on PI monotherapy during follow-up (defined as VF or an early discontinuation of PI monotherapy for any reason, including loss to follow-up). We also recorded the reasons for the discontinuation of treatment and evaluated the relationship between VF or TF and the presence of blips, treatment

with lopinavir/ritonavir versus darunavir/ritonavir monotherapy, CD4+ nadir, prior failure with PIs and duration of virological suppression before the initiation of PI monotherapy. Finally, we evaluated data on adherence and protease resistance mutations (IAS-USA 2013 Drug Resistance Mutations)\textsuperscript{20} in patients experiencing VF.

Variables were described using the median and IQR and compared using the Mann–Whitney test. Percentages were compared using the \(\chi^2\) test or Fisher’s exact test where appropriate. Life table survival analysis was used to calculate the cumulative VF and TF at 48 and 96 weeks. HRs and 95% CIs were also calculated and Cox regression was applied to assess the effect of several factors on the risk of developing VF and TF. Multivariate models were fitted using 0.05 as the significance level for a covariate to be included in the final model. Differences were considered statistically significant at \(P<0.05\). The statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) and Stata 12 (StataCorp, College Station, TX, USA).

Results

Baseline characteristics

ART was simplified to PI monotherapy in 522 patients between November 2003 and June 2012 (lopinavir/ritonavir in 309 and darunavir/ritonavir in 213). Patients had had an undetectable pVL for a mean of 166.4 (142.9) weeks before starting PI monotherapy, 141 (27.0%) patients had hepatitis C virus (HCV) co-infection and 94 (18.0%) had a prior history of VF while receiving PI-based ART. In addition, the previous ART regimen included PIs in 395 (75.7%) patients and the same PIs as in the monotherapy regimen in 245 (46.9%) patients. The reasons for switching to PI monotherapy were treatment simplification in 297 (56.9%) patients, ART-related toxicity in 135 (25.9%) patients and other causes in 90 (17.2%) patients. Patients were followed for a median (IQR) of 64.3 (30.5–143.0) weeks. The follow-up was longer in patients on lopinavir/ritonavir than in those on darunavir/ritonavir \[85.9 (38.1–179.1)\] weeks and 48.9 (26.1–100.7) weeks, respectively; \(P<0.001\). Other demographic and clinical characteristics of the patients at baseline are summarized in Table 1.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Age (years), median (IQR)</th>
<th>General cohort (n = 522)</th>
<th>DRVr monotherapy (n = 213)</th>
<th>LPVr monotherapy (n = 309)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>470 (42–52)</td>
<td>470 (41.0–51.0)</td>
<td>470 (42.0–52.0)</td>
<td>0.062</td>
</tr>
<tr>
<td>HCV co-infection, n (%)</td>
<td>376 (72.0)</td>
<td>151 (70.9)</td>
<td>225 (72.8)</td>
<td>0.845</td>
</tr>
<tr>
<td>No. of prior ART regimens, median (IQR)</td>
<td>141 (27.0)</td>
<td>54 (25.4)</td>
<td>87 (28.2)</td>
<td>0.268</td>
</tr>
<tr>
<td>Prior failure to PI, n (%)</td>
<td>5.0 (2–8)</td>
<td>4 (2–7)</td>
<td>5 (2–8)</td>
<td>0.015</td>
</tr>
<tr>
<td>PI at entry, n (%)</td>
<td>96 (18.0)</td>
<td>30 (14.1)</td>
<td>64 (20.7)</td>
<td>0.063</td>
</tr>
<tr>
<td>NNRTI at entry, n (%)</td>
<td>395 (75.7)</td>
<td>154 (72.3)</td>
<td>241 (77.9)</td>
<td>0.137</td>
</tr>
<tr>
<td>Same PI used at entry, n (%)</td>
<td>24 (4.6)</td>
<td>13 (6.1)</td>
<td>11 (3.6)</td>
<td>0.173</td>
</tr>
<tr>
<td>Years on ART, median (IQR)</td>
<td>10.3 (4.5–14.0)</td>
<td>9.9 (3.1–14.1)</td>
<td>10.5 (6.6–13.4)</td>
<td>0.361</td>
</tr>
<tr>
<td>Time with virological suppression (weeks), median (IQR)</td>
<td>129.3 (52.7–249.1)</td>
<td>123.1 (60.4–260.0)</td>
<td>122.1 (58.3–248.0)</td>
<td>0.868</td>
</tr>
</tbody>
</table>

LPVr, lopinavir/ritonavir; DRVr, darunavir/ritonavir.
Effectiveness

Of the 522 patients included during the follow-up, 89 (17.0%) experienced toxicities that led to the discontinuation of PI monotherapy, 61 (11.7%) developed VF, 53 (10.2%) were switched to different ART regimens for other reasons and 3 (0.6%) interrupted PI monotherapy voluntarily (Table 2). Blips were observed for 92 (17.6%) patients during follow-up. The cumulative survival analysis showed that 94% (95% CI 91%–96%) and 79% (95% CI 75%–82%) of patients, respectively, were free of VF and TF at Week 48. At Week 96, the percentage of patients free of VF and TF was 86% (95% CI 81%–89%) and 62% (95% CI 57%–67%), respectively.

The clinical outcomes for lopinavir/ritonavir and darunavir/ritonavir monotherapy are shown in Table 2. The survival analysis showed that the percentage of patients on lopinavir/ritonavir who were free of VF at 48 and 96 weeks was 94% (95% CI 90%–96%) and 86% (95% CI 81%–90%), respectively; the percentage of patients on darunavir/ritonavir who were free of VF at 48 and 96 weeks was 93% (95% CI 88%–96%) and 85% (95% CI 77%–90%), respectively (HR = 1.0, 95% CI 0.6–1.8; P = 0.962) (Figure 1a). No significant association was observed between VF and the occurrence of blips, a CD4+ nadir <100 cells/mm³, prior failure with PIs or a duration of virological suppression <24 weeks. The percentage of patients on lopinavir/ritonavir who were free of TF at 48 and 96 weeks was 76% (95% CI 71%–81%) and 59% (95% CI 53%–65%), respectively; the percentage of patients on darunavir/ritonavir who were free of TF at 48 and 96 weeks was 86% (95% CI 76%–88%) and 68% (95% CI 59%–75%), respectively (Figure 1b). Patients on lopinavir/ritonavir monotherapy had a 1.5-fold greater risk (95% CI 1.1–2.1; P = 0.012) of experiencing TF during follow-up than those on darunavir/ritonavir of experiencing adverse events leading to a discontinuation of treatment (HR = 2.3, 95% CI 1.3–3.9; P = 0.003).

No cases of HIV-related encephalopathy or other serious CNS adverse events leading to a discontinuation of treatment were observed.

Safety

Adverse events were registered as the main reason for the discontinuation of treatment in 73/309 (23.6%) patients on treatment with lopinavir/ritonavir and in 16/213 (7.5%) patients receiving darunavir/ritonavir (Table 2). The most frequent adverse events leading to treatment discontinuation were gastrointestinal disturbances [39/89 (43.8%) patients] and dyslipidaemia [34/89 (38.2%) patients]. The adverse events were usually mild and none was Grade 3–4. Patients on lopinavir/ritonavir were at significantly greater risk than those on darunavir/ritonavir of experiencing adverse events leading to a discontinuation of treatment (HR = 2.3, 95% CI 1.3–3.9; P = 0.003).

No cases of HIV-related encephalopathy or other serious CNS adverse events leading to a discontinuation of treatment were observed.

Drug resistance

Genotyping data were available during follow-up for 19 (31.1%) patients with VF (13 on lopinavir/ritonavir and 6 on darunavir/ritonavir). Ten (52.6%) patients had a history of failure to PIs. Major IAS-USA protease-associated mutations were observed in the genotype of four patients who experienced VF, minor IAS-USA protease-associated mutations were reported in six genotypes and no protease-associated mutations were found in nine genotypes.

Historical genotypes to establish comparisons were not available for three patients on lopinavir/ritonavir monotherapy and major protease-associated mutations were detected in the genotyping test at the failure of monotherapy. In the first case, there were no records of prior failures to PIs, but the mutations L10V, I13V, G16E, E35D, M36I, R41K, L63T, H69K, V82A and L89M were
Discussion

Our data suggest that the simplification of treatment to PI monotherapy maintains virological suppression in clinical practice. Although the rates of VF were similar for lopinavir/ritonavir and darunavir/ritonavir monotherapy, the latter was significantly more effective than the former. Withdrawals due to adverse effects were the main reason for this difference.

Consistent with the results from clinical trials and from a large Spanish observational cohort study,19,21–23 few patients in our study developed VF. In addition, we found no differences in the risk of developing VF between lopinavir/ritonavir and darunavir/ritonavir monotherapy, and high rates of viral resuppression were observed after failure. Resuppression was achieved with various ART regimens, although rescue regimens based exclusively on addition of NRTIs were less common. This approach differs considerably from that of clinical trials.21–23

Adverse events were the main reason for the discontinuation of treatment in our study and were significantly more common in patients receiving lopinavir/ritonavir. These results are in contrast to those of Pulido et al., who performed a clinical trial with lopinavir/ritonavir monotherapy,12 in which no discontinuations due to toxicity were recorded. It is important to note, however, that the trial participants were already on a stable lopinavir/ritonavir–containing regimen. In our study, although 63% of the patients who switched to lopinavir/ritonavir monotherapy were already on stable treatment with this drug, we observed a higher risk of discontinuations because of lopinavir/ritonavir–related adverse events. By contrast, and consistent with the findings of previous clinical trials, few discontinuations due to adverse events were recorded in patients treated with darunavir/ritonavir monotherapy.13,14 These results reflect the well-known better safety profile of darunavir/ritonavir in comparison with lopinavir/ritonavir-based regimens.24,25

In several trials, the factors associated with VF to PI monotherapy include suboptimal adherence, a CD4+ nadir <100 cells/mm3, a shorter time with virological suppression and the presence of HCV co-infection.26–29 Although adherence to treatment was not systematically reviewed in our study, clinical records showed that adherence was poor in most patients who experienced VF. In addition, we were not able to find a significant relationship between the virological response and the CD4+ nadir, the previous time with virological suppression and the presence of HCV co-infection.18,19,26–28 Consistent with the findings of other authors18,19 and even though the number of patients for whom treatment with PIs failed was too small to detect differences between the two monotherapies, it is interesting that we did not find a significant relationship between prior failure to PIs and VF. Nevertheless, some PI resistance–associated mutations were detected after failure in a small percentage of these patients. Therefore, the recommendation to use PI monotherapy only in patients with no previous failure of a PI-based regimen1,2,12–15 seems to be prudent and reasonable.

One potential concern about PI monotherapy is its ability to maintain control of viral replication in different body compartments. Indeed, the ability of PI monotherapy to maintain virological suppression in the CNS and the potential risk of neurocognitive impairment are still controversial topics.30–33 In addition, a few cases of HIV-related encephalopathy have been reported.19,34 Although the design of our study does not enable us to address this issue...
and only reports from clinical records were available, we did not observe cases of HIV-related encephalopathy or other serious CNS events, a finding which is consistent with those of most clinical trials.12–14,21,22

Our study is subject to a series of limitations. First, its retrospective and uncontrolled design and differences in some baseline characteristics might have introduced bias or unmeasurable confounding factors that could in part explain our results. Second, the different lengths of follow-up for the two drugs made it difficult to establish comparisons between lopinavir/ritonavir and darunavir/ritonavir. Although our results were adjusted for length of follow-up in the survival analyses, the results of direct comparisons between lopinavir/ritonavir and darunavir/ritonavir should be interpreted with caution. Finally, treating physicians could have had the feeling that darunavir/ritonavir was better tolerated than lopinavir/ritonavir, thus introducing bias in the results for lopinavir/ritonavir toxicity. The key strength of our study is that it provides insights into differences between lopinavir/ritonavir and darunavir/ritonavir monotherapy in clinical practice: lopinavir/ritonavir is less effective than darunavir/ritonavir owing to the latter’s well-known and more favourable safety profile.26,25 In contrast to international HIV guidelines, which recommend lopinavir/ritonavir or darunavir/ritonavir indiscriminately as an alternative strategy in selected patients,2,15 our findings suggest that once-daily darunavir/ritonavir monotherapy might be the preferred choice for PI monotherapy.

In conclusion, monotherapy with lopinavir/ritonavir or darunavir/ritonavir seems to be safe and effective in HIV-1-infected patients with sustained viral suppression in clinical practice. However, better tolerability and convenience of administration suggest that darunavir/ritonavir might be the preferred option for PI monotherapy. The proper selection of candidates for PI monotherapy is mandatory in order to minimize the risk of VF.

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Simplification with PI monotherapy


