Short Communication: Efficacy and Safety of Treatment Simplification to Lopinavir/Ritonavir or Darunavir/Ritonavir Monotherapy: A Randomized Clinical Trial

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Abstract

Antiretroviral treatment simplification strategies based on monotherapy with darunavir/ritonavir (DRV/r) or lopinavir/ritonavir (LPV/r) have not been directly compared in clinical trials. We evaluated the 48-week efficacy and safety of DRV/r versus LPV/r monotherapy as a treatment simplification strategy in a multicenter, randomized open-label study. Maintenance of viral suppression in cerebrospinal fluid (CSF) and semen was also explored. An intention to treat efficacy analysis was performed considering missing equals to failure (ITT:M = F). Virological failure (VF) was defined as a confirmed increase in plasma HIV-1 RNA >50 copies/mL. A total of 75 patients were enrolled: 40 were allocated to DRV/r and 33 to LPV/r. In the ITT: M = F analysis, 77.5% of patients on DRV/r and 66.6% of patients on LPV/r maintained HIV-1 RNA <50 copies/mL at week 48 (p = .302, treatment difference 10.8% [95% CI, –12.6 to 34.2]). In the DRV/r arm, no patients developed VF and 15.0% discontinued treatment due to adverse events. In the LPV/r arm, 2 (6.1%) patients developed VF and 18.2% discontinued monotherapy due to adverse events. Gastrointestinal disturbances were experienced by 18.2% and 2.5% of patients in the LPV/r and DRV/r arms, respectively (p = .019). Two patients had detectable HIV-1 RNA ≥50 copies/mL in CSF or semen. Monotherapy with LPV/r or DRV/r seems to be virologically effective in selected HIV-1-infected patients with sustained viral suppression. Differences between both regimens seem driven mainly by the better tolerability profile of DRV/r.

Monotherapy with darunavir/ritonavir (DRV/r) or lopinavir/ritonavir (LPV/r) in suppressed HIV-infected patients has become an attractive NRTI-sparing strategy.1–3 While the approach maintains virological suppression in selected patients, tolerance and safety profiles seem to be different.4–11 Monotherapy with DRV/r or LPV/r has not been directly compared in a randomized clinical trial. Therefore, we designed a prospective, randomized, open-label noninferiority trial (LOPIDAR NCT00994344) to compare the efficacy and safety of DRV/r and LPV/r monotherapy as a simplification strategy in HIV-infected patients with sustained viral suppression on stable triple antiretroviral therapy (ART). The local institutional review boards approved the protocol, and participants provided informed consent.

Inclusion criteria: HIV-infected adults (≥18 years old), virological suppression (plasma HIV-1 RNA <50 copies/mL), stable ART for 90 days before entry, CD4+ nadir ≥100 cells/mm³, and absence of PI resistance-associated mutations. Exclusion criteria: history of virological failure (VF) to previous PI-containing regimens, HBV coinfection, and concomitant use of drugs that interacted with the study drugs at inclusion.

Patients were randomly assigned to receive once-daily DRV/r 800/100 mg or twice-daily LPV/r 400/100 mg at baseline according to the data in the prescribing and labeling information of LPV/r and results from previous clinical trials.12–14 Demographic and clinical characteristics, self-reported adherence, plasma HIV-1 RNA, CD4+ count, and...
routine laboratory parameters were registered at baseline and every 12 weeks thereafter until week 48. We also evaluated reasons for discontinuation and results of genotyping in patients experiencing VF. HIV-RNA was measured in cerebrospinal fluid (CSF) and semen in a subgroup of patients at baseline and at week 48 using AmpliPrep/COBAS TaqMan HIV-1 Test, v2.0 (Roche Molecular Systems, Inc.).

The primary endpoint was the percentage of patients who maintained virological suppression in plasma at week 48. VF was defined as a confirmed increase in plasma HIV-1 RNA >50 copies/mL. Secondary endpoints were the percentage of patients who discontinued monotherapy owing to adverse events, changes in laboratory parameters (creatinine, cholesterol [total, HDL, and LDL], triglycerides, liver enzymes, and CD4+), and resistance to PI in patients experiencing VF. Moreover, the percentage of patients who maintained viral suppression in CSF and semen was evaluated in the subgroup of patients.

The per protocol estimation was that a sample size of 51 individuals per group would provide 80% power to detect differences in the proportion of viral suppression in subjects receiving DRV/r or LPV/r monotherapy, assuming proportions of efficacy of 100% and 95%, a noninferiority limit of 12%, a 5% loss to follow-up, and a 1-sided z value of .05. Although a sample of 102 patients was initially estimated as necessary to provide adequate statistical power to ascertain whether DRV/r was noninferior to LPV/r, inclusion had to be stopped after 192 weeks because there were no more eligible patients. We present the efficacy and safety results using available data.

A total of 75 patients were enrolled. Two patients withdrew consent before initiation of the study medication and were excluded. Forty patients were allocated to DRVr and 33 patients to LPVr. Sixty patients (82%) were men, median interquartile range (IQR) age was 43 (34–47) years, and 14 (19%) patients had HCV coinfection. Median (IQR) time since diagnosis of HIV infection was 108 (35–197) weeks. The previous ART regimen already included a PI in 56 (77%) patients. At baseline, 31 (42%) patients were taking the same PI as in the randomized monotherapy regimen. However, in the LPV/r arm, more patients than in the DRV/r arm were already receiving the same PI at randomization (p = .015).

In the DRV/r arm, no patients developed VF, 6 (15.0%) discontinued treatment owing to adverse events, and 3 (7.5%) were lost to follow-up. In the LPV/r arm, 2 (6.1%) patients developed VF (HIV-1 RNA of 140 and 105 copies/mL at weeks 24 and 48, respectively, with nonamplifiable genotypes), 6 (18.2%) discontinued monotherapy owing to adverse events, 2 (6.1%) were lost to follow-up, and 1 (3.0%) withdrew voluntarily. Therefore, 31/40 (77.5%) patients on DRV/r and 22/33 (66.6%) patients on LPV/r maintained HIV-1 RNA <50 copies/mL at week 48 (p = .302, treatment difference 10.8% [95% CI, −12.6 to 34.2]) in the efficacy analysis (ITT:M = F).

Twelve (16.4%) patients discontinued ART because of nonserious adverse events. No serious CNS adverse events were observed. Gastrointestinal disturbances were experienced by 6/33 (18.2%) and 1/40 (2.5%) patients in the LPV/r and DRV/r arms, respectively (p = .019).

There were no significant differences in the lipid profile between the groups at week 48 (Table 1). No differences were observed in the proportion of patients taking tenofovir and lipid-lowering drugs. No significant differences were detected for creatinine, liver enzymes, or CD4+ count (Table 1).

HIV-RNA was undetectable in CSF in 15/15 (100%) patients at baseline. At 48 weeks, 8 (53.3%) patients maintained virological suppression in CSF, 4 (26.7%) patients had no CSF samples, 2 (13.3%) did not provide samples because of VF, and 1 (6.7%) had a confirmed CSF HIV-RNA of 75 copies/mL with undetectable levels in plasma and semen. Semen samples were obtained in 13 patients at baseline. Of these, 12 (92.3%) had undetectable HIV-RNA and 1 (7.7%) had a confirmed HIV-RNA of 365 copies/mL, while CSF and plasma HIV-RNA levels were undetectable. Seven (53.8%) patients had no samples available at 48 weeks, 4 (30.7%) maintained virological suppression, and 2 (15.4%) were not tested owing to VF in plasma.

Our data suggest that simplification to PI monotherapy maintains virological suppression with no difference in efficacy between DRV/r and LPV/r at 48 weeks. Consistent with previous clinical and observational studies, there were few VFs and adverse events were the main reason for discontinuation, with differences in the safety profiles of DRV/r and LPV/r.6,9–11 Gastrointestinal disturbances leading to

### Table 1. Differences in Laboratory Parameters Between Arms (n = 73)

<table>
<thead>
<tr>
<th></th>
<th>DRVr monotherapy (n = 40)</th>
<th>LPVr monotherapy (n = 33)</th>
<th>p^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 48</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.5 (3.9–5.2)</td>
<td>5.1 (4.5–6.7)</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.2 (1.0–1.4)</td>
<td>1.3 (1.1–1.5)</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>2.7 (2.2–3.1)</td>
<td>2.8 (2.6–3.6)</td>
<td></td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.3 (1.0–1.7)</td>
<td>1.5 (1.0–2.2)</td>
<td></td>
</tr>
<tr>
<td>CD4+ count, cells/mm³</td>
<td>629 (448–891)</td>
<td>628 (478–819)</td>
<td></td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>24 (14–37)</td>
<td>26 (16–39)</td>
<td></td>
</tr>
<tr>
<td>AST, U/L</td>
<td>22 (19–29)</td>
<td>24 (19–32)</td>
<td></td>
</tr>
<tr>
<td>Creatinine, umol/L</td>
<td>79.5 (71.3–85.5)</td>
<td>79.0 (65.5–85.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 48</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.0 (4.2–5.9)</td>
<td>5.5 (4.5–6.3)</td>
<td>0.110</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.3 (1.0–1.5)</td>
<td>1.1 (0.9–1.7)</td>
<td>0.746</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>2.9 (2.2–3.3)</td>
<td>2.9 (2.2–3.3)</td>
<td>0.335</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.7 (1.1–1.9)</td>
<td>1.6 (1.3–2.8)</td>
<td>0.192</td>
</tr>
<tr>
<td>CD4+ count, cells/mm³</td>
<td>593 (471–831)</td>
<td>652 (570–887)</td>
<td>0.329</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>29 (19–36)</td>
<td>19 (17–44)</td>
<td>0.693</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>25 (21–32)</td>
<td>21 (17–33)</td>
<td>0.202</td>
</tr>
<tr>
<td>Creatinine, umol/L</td>
<td>76.0 (65.0–86.0)</td>
<td>70.0 (55.2–83.5)</td>
<td>0.194</td>
</tr>
</tbody>
</table>

^aAll values are expressed as median (interquartile range).

^bComparisons between arms at 48 weeks.

DRVr, darunavir/ritonavir; LPVr, lopinavir/ritonavir; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
discontinuation were significantly more frequent with LPV/r. Although we did not observe differences in the lipid profile between the groups, a higher number of patients allocated to LPV/r monotherapy were already receiving LPV/r-based triple therapy at randomization and may therefore have been able to tolerate LPV/r without lipid abnormalities. Despite the very limited number of available samples, virological rebound in CSF or semen was uncommon after initiation of monotherapy. This finding is consistent with those of previous reports, suggesting that virological rebound in body compartments may be infrequent in patients on PI monotherapy.

As for limitations, our study was underpowered to demonstrate noninferior efficacy of LPV/r versus DRV/r (statistical power of 77.12%, alpha error of 5%, beta error of 0.26%, and noninferiority limit of 12%). In addition, detection of safety issues could have been affected, and early interruption could have unbalanced the groups. Nevertheless, to our knowledge, this is the first randomized study to compare two PIs in monotherapy for simplification and simultaneously explore maintenance of virological suppression in different body compartments. In conclusion, monotherapy with LPV/r or DRV/r seems to be virologically effective in selected HIV-1-infected patients with sustained viral suppression. Differences between both treatments seem driven mainly by the better tolerability profile of DRV/r.

Acknowledgments

This study was supported in part by grants from Lluita contra la SIDA Foundation (Barcelona, Spain), the Spanish AIDS Network “Red Temática de Investigación en SIDA” (RIS, RD06/0006), and GRBIO (Grupo de Recerca en Bioestadística i Bioinformàtica; 2014 SGR 464). The funders had no role in the study design, data collection and analysis, the decision to publish, or drafting of the article. The authors are grateful to Thomas O’Boyle for editorial assistance.

Author Disclosure Statement

J.R.S. has received research funding, consultancy fees, and lecture sponsorships from and has served on advisory boards for Abbott, Boehringer Ingelheim, Gilead Sciences, GlaxoSmithKline, Janssen-Cilag, Bristol-Myers Squibb, Merck Sharp & Dohme, and Viiv Healthcare.

J.M.L. has received research funding, consultancy fees, and lecture sponsorships from and has served on advisory boards for Abbott, Boehringer Ingelheim, Gilead Sciences, GlaxoSmithKline, Janssen-Cilag, Merck Sharp & Dohme, Pfizer, and Viiv Healthcare.

R.P. has received research funding and consultancy fees from and has served on advisory boards for Boehringer Ingelheim, Gilead Sciences, GlaxoSmithKline, Janssen-Cilag, Merck Sharp & Dohme, Pfizer, and Viiv Healthcare.

B.C. has received research funding, consultancy fees, and lecture sponsorships from and has served on advisory boards for Abbott, Boehringer Ingelheim, Gilead Sciences, GlaxoSmithKline, Janssen-Cilag, Merck Sharp & Dohme, Panacos, Pfizer, Roche, and Tibotec.

J.M. has received research funding, consultancy fees, and lecture sponsorships from and has served on advisory boards for Abbott, Boehringer Ingelheim, Gilead Sciences, GlaxoSmithKline, Janssen-Cilag, Bristol-Myers Squibb, Viiv Healthcare, and Pfizer.

I.B., N.P.A., D.G.R., and M.C. declare that they have no conflicts of interest.

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