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Long-term safety and effectiveness of lopinavir/ritonavir in antiretroviral-experienced HIV-1-infected children

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ABSTRACT

Aim To evaluate the long-term safety and effectiveness of lopinavir/ritonavir (LPV/r) in a population-based cohort of HIV-1-infected children.

Methods All children enrolled in the Swiss Mother and Child HIV Cohort Study, treated with LPV/r-based combination antiretroviral treatment (cART) between November 2000 and October 2008, were included. Results 88 children (25 [28%] protease inhibitor (PI)-naive, 16 [18%] ART-naive) were analysed (251 patient-years on LPV/r). After 48 weeks on LPV/r, 70 children had a median (interquartile range (IQR)) decrease in HIV-1 viral load of 4.25 log (5.45–3.17; PI-naive, n=17) and 2.53 (3.68–1.38; PI-experienced, n=53). Median (IQR) increase in CD4 count was 429 (203–593; PI-naive) and 177 (21–331; PI-experienced) cells/μl. These effects remained stable throughout 192 weeks for 25 children. Treatment was stopped for viral rebound in seven and suspected toxicity in 12 children.

Conclusion Long-term treatment with LPV/r-based cART is safe and effective in HIV-1-infected children.

INTRODUCTION

Combination antiretroviral therapy (cART) significantly reduces mortality in HIV-infected children. One class of antiretroviral drug commonly used in cART are the protease inhibitors (PIs). These drugs are now mostly given with ritonavir, which inhibits their metabolism and boosts PI levels. Recently, our group reported on the long-term safety and effectiveness of mainly unboosted PI-based cART in HIV-1-infected children enrolled in the Swiss Mother and Child HIV Cohort Study (MoCHiV).1 As boosted PIs have now become the line and the percentage of patients with suppressed HIV-1 replication were summarised at each time point. Patients who stopped LPV/r before the examined time point or had insufficient follow-up were either excluded from the analysis at that time point or, as a sensitivity analysis, we carried the last available measurement forward and imputed it for all subsequent time points (last observation carry forward).

In patients with detectable viral loads when starting LPV/r, we determined the time to complete virological suppression (defined as the first of two consecutive measurements of <50 copies/ml) or time to stopping LPV/r without virological suppression, whichever came first, using cumulative incidence functions. Viral rebound was defined as the first of two consecutive HIV-1 RNA loads of >400 copies/ml or one HIV-1 RNA load of >400 copies/ml plus a subsequent cessation of LPV/r within 91 days.

PATIENTS AND METHODS

HIV-1-infected children living in Switzerland are prospectively followed by MoCHiV2 according to a common protocol and by use of structured data collection forms. Ethics approval was granted by the cantonal ethical committees of each participating centre and written informed consent of participants’ caregivers is obtained before inclusion. As outlined elsewhere,1 children were seen before starting or changing cART and at weeks 4 and 12, and every 12 weeks thereafter. The dosage of LPV/r was 300 mg/75 mg/m² twice daily for all children (adult dose for those ≥13 years of age). Adherence was assessed by self-declaration at each visit (five possible answers for the number of missed doses). Adverse events and abnormal laboratory results (DAIDS grade 3 or 4)3 during LPV/r treatment were considered as possible side effects, however treatment decisions were left to the treating physician’s assessment. Reasons for switching or stopping treatment were verified by chart review.

All children <18 years of age treated with LPV/r between November 2000 (paediatric approval) and October 2008 were included. Children were defined as PI-naive if they had not received PI previously, and PI-experienced if they had been given PI as part of previous cART.

Plasma HIV-1 RNA loads were determined in real time using the Amplicor HIV Monitor kit (Roche, Basel, Switzerland) and CD4 cells using flow cytometry. HIV-1 replication was considered suppressed if HIV-1 RNA was <50 copies/ml.

Data analysis

We analysed the first LPV/r treatment episode for each child, unless it lasted <30 days and was followed by a subsequent longer episode, which was then examined instead. Baseline was defined as the time of initiation of the examined LPV/r episode.

Immunological and virological responses were analysed at 6-monthly (24-week) intervals. Median (interquartile range (IQR)) changes from baseline and the percentage of patients with suppressed HIV-1 replication were summarised at each time point. Patients who stopped LPV/r before the examined time point or had insufficient follow-up were either excluded from the analysis at that time point or, as a sensitivity analysis, we carried the last available measurement forward and imputed it for all subsequent time points (last observation carry forward).
RESULTS

Our analysis included the first LPV/r treatment episode of 84 children and the second (after a preceding episode of <30 (9–17) days of four children (251 patient-years). Baseline characteristics are summarised in table 1.

Twenty-five children (28%) were PI-naive including 16 (18%) who had never had any antiretroviral therapy. Seven PI-naive children had previously had other ART for a median time of 1.6 (IQR 0.7–3.1) years, (zidovudine alone (n=3) or in combination with lamivudine (n=2), or non-PI based cART (n=2)).

Sixty-three (72%) children were PI-experienced (142 treatment episodes; ritonavir (n=28), nelfinavir (n=17) or both (n=18)). Median time from the first PI-based regimen until treatment with LPV/r was 4.3 (IQR 3.2–6.1) years. Earlier PI treatments were most frequently combined with lamivudine/zidovudine (42 episodes) or lamivudine/stavudine (22 episodes). The median duration of a LPV/r treatment episode was estimated at 3.86 (95% CI 2.61 to 5.19) years.

Virological and immunological responses

This analysis was based on 70 (17 PI-naive, 53 PI-experienced) patients for whom baseline and at least one follow-up measurement of HIV-1 RNA and CD4 cells was available (figure 1).

Of 61 patients with detectable viral load when starting LPV/r, 40 (66%) achieved complete viral suppression (13/15 (87%) PI-naive and 27/46 (59%) PI-experienced children). Median (IQR) time to full suppression was 180 (153–211) days in PI-naive and 152 (95–242) days in PI-experienced children. Fifteen patients (25%; two PI-naive, 13 PI-experienced) stopped LPV/r before reaching complete viral suppression. After 48 weeks of LPV/r, median (IQR) decreases in viral load were 4.25 (5.45–3.17) in PI-naive and 2.53 (3.68–1.38) in PI-experienced patients.

Of 49 children with complete viral suppression (including nine suppressed at baseline), viral rebound occurred in four PI-naive and three PI-experienced children during 124 patient-years of follow-up (5.65 events per 100 patient-years). Median time to viral rebound was 2.18 (range 1.63–3.72 years; 2.59 (2.17–3.72) in PI-naive and 1.85 (1.63–2.75) years in PI-experienced children.

After 48 weeks of LPV/r, median (IQR) increases in CD4 counts and CD4 percentages were 429 (203–593) cells/µl and 10% (3–18%) in PI-naive and 177 (21–331) cells/µl and 6% (2–9%) in PI-experienced patients.

TREATMENT INTERRUPTIONS AND SIDE EFFECTS

Forty-two children (48%), including seven with viral rebound and 12 with possible toxicity, stopped their LPV/r-based regimen during follow-up. For the remaining 23 children, the reasons for stopping treatment were: withdrawal from the cohort (n=7), patient’s or physician’s wish or decision (n=6 and n=4, respectively), structural treatment interruption (n=3) and unknown (n=3).

Among the 12 children with suspected toxicity, adverse events were: gastrointestinal in five (including liver and pancreas in one each), and related to fat redistribution, the nervous system, the endocrine system, cardiovascular disease, hypersensitivity, blood count abnormality and unspecified in one each. Grade 3 or 4 laboratory abnormalities were documented in 27 children, but only three children stopped LPV/r (thrombocytopenia (11×109/l without recovery after treatment cessation), a liver enzyme elevation (aspartate aminotransferase 185 IU/l) and an amylase elevation (870 IU/ml without elevation of serum lipase) in one each). Eleven of the 12 children with suspected toxicity restarted a LPV/r-based cART again after a median (IQR) interval of 0.98 (0.52–2.79) years. We observed no deaths on LPV/r.

DISCUSSION

The goal of the present study was to address the long-term safety and effectiveness of LPV/r-based cART in a population-based cohort of HIV-1-infected children.

Our results show similar proportions of children with undetectable viral loads after 48 weeks as in the initial phase

Table 1 Baseline characteristics of 88 HIV-1-infected children receiving lopinavir boosted with ritonavir (LPV/r)

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>Summary statistic†</th>
<th>Protease inhibitor (PI)-naive children (N=25)</th>
<th>PI-experienced children (N=63)</th>
<th>All children (N=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>4.80 (2.86, 9.91)</td>
<td>11.63 (7.82, 14.47)</td>
<td>10.21 (6.36, 14.32)</td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>13 (52%)</td>
<td>38 (60%)</td>
<td>51 (58%)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>3 (12%)</td>
<td>35 (56%)</td>
<td>38 (43%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>7 (28%)</td>
<td>19 (30%)</td>
<td>26 (30%)</td>
<td></td>
</tr>
<tr>
<td>Hispano American</td>
<td>1 (4%)</td>
<td>4 (6%)</td>
<td>5 (6%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (4%)</td>
<td>2 (3%)</td>
<td>3 (3%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>13 (52%)</td>
<td>3 (5%)</td>
<td>16 (18%)</td>
<td></td>
</tr>
<tr>
<td>Route of HIV-1 infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perinatal</td>
<td>17 (68%)</td>
<td>59 (94%)</td>
<td>76 (86%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (32%)</td>
<td>4 (6%)</td>
<td>12 (14%)</td>
<td></td>
</tr>
<tr>
<td>Prior AIDS-defining condition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 cell count (cells/µl)†</td>
<td>402 (245, 826)</td>
<td>459 (289, 837)</td>
<td>434 (277, 859)</td>
<td></td>
</tr>
<tr>
<td>CD4 percentage†</td>
<td>20 (12, 28)</td>
<td>22 (16, 32)</td>
<td>22 (15, 30)</td>
<td></td>
</tr>
<tr>
<td>HIV-1 viral load (log_{10} RNA copies/ml)†</td>
<td>5.41 (4.38, 5.67)</td>
<td>4.16 (2.70, 5.03)</td>
<td>4.34 (2.90, 5.26)</td>
<td></td>
</tr>
</tbody>
</table>

*Time-dependent covariates evaluated at the time of LPV/r initiation.
†Median (IQR) for continuous variables, n (%) for categorical variables.
‡CD4 cell count, CD4 percentage and HIV-1 viral load at LPV/r initiation (within −91/+30 days) were missing for 16, 19 and 14 children, respectively.
Drug therapy was introduced into clinical use later than these other PIs, direct comparison is not feasible. Of note, median time to achieve viral suppression seems to be much longer in children than in adults.4

The proportion of children stopping cART (48%) for various reasons was higher than reported elsewhere.5 However, treatment failure (n=7) and toxicity (n=12) accounted for only 45% of this group. Laboratory abnormalities were associated

Figure 1 Median (solid lines) and quartiles (dashed lines) of changes in CD4 cell count from baseline. The grey shaded area indicates the percentage of patients with suppressed HIV-1 viral load. Top panels: results based on actual HIV-1 viral load and CD4 cell counts at the respective week (n is the number of patients under follow-up and ongoing lopinavir boosted with ritonavir (LPV/r) therapy at the respective week). Bottom panels: results based on carry-forward of the last available HIV-1 viral load and CD4 cell count while on LPV/r for each patient. LOCF, last observation carry forward; LPV/r, lopinavir/ritonavir; PI, protease inhibitor.
with only three children who stopped treatment. Most children with suspected clinical toxicities re-started LPV/r-based regimens. Limitations of our study include the fact that adherence was only assessed by self-declaration and viral resistance and drug levels were not routinely examined.

In conclusion, our data indicate that long-term treatment with LPV/r-based cART is well tolerated, safe and effective in HIV-1-infected children.


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Competing interests None.

Ethics approval This study was conducted with the approval of the cantonal ethics committees of all involved treatment centres.

Provenance and peer review Not commissioned; externally peer reviewed.

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