1.0 Abstract

Title

ProSpective, MultI-Center, Observational PrograM to Assess the Effectiveness of Dual TheraPy (Lopinavir/ritonavir+LamivudinE) in Treatment-Experienced HIV Infected Patients in the Routine Clinical Settings of the Russian Federation (SIMPLE)

Keywords

Dual therapy, HIV-1, viral load, drug resistance, lopinavir/ ritonavir, lamivudine.

Rationale and Background

Standard of care treatment of HIV-1-infected patients is usually associated with the use of a triple antiretroviral therapy (ART) with regimens including two nucleos(t)ide analogues (NRTIs). NRTIs are not always well-tolerated (short and long term). For example, some NRTIs can cause anemia (zidovudine)[1], neurotoxicity and lipodystrophy (stavudine and didanosine)[2] and kidney dysfunction (tenofovir)[3]. Cardiovascular disease is also associated with abacavir in some cohort studies[4]. Lamivudine (3TC) is an effective NRTI with good safety profile that has been widely used as a first line drug for the treatment of HIV infected adults and children. The antiviral potency of LPV/r (lopinavir/ritonavir) has been clearly demonstrated in a wide spectrum of patients in a number of different clinical trials, for periods of up to seven years[5].

LPV/r+3TC dual therapy has been studied in HIV-1-naïve and HIV-1 experienced patients in the GARDEL and OLE studies respectively. Over 48 weeks, LPV/r+3TC demonstrated non-inferior efficacy and comparable safety to LPV/r+2 NRTIs, as first line regimen in GARDEL study and as maintenance therapy in virologically suppressed patients in OLE study[6-9].

Efficacy data for LPV/r+3TC dual therapy data from treatment-experienced HIV-1 populations are overwhelmingly from the OLE study whereas no data exists on that effectiveness of LPV/r+3TC in treatment-experienced HIV-1 infected patients in routine clinical settings of the Russian Federation.

Research Question and Objectives

Primary Objective

To assess the virologic effectiveness of dual therapy (lopinavir/ ritonavir (LPV/r)+lamivudine (3TC)) in a population of treatment-experienced HIV-1 infected patients with an undetectable plasma HIV-1 RNA level (<50 copies/mL for at least 6 months) at the 48-week time point of treatment in the routine clinical settings of the Russian Federation.

Secondary Objectives

1. To evaluate the virologic effectiveness of dual therapy at week 24;
2. To evaluate the immune reconstitution on the dual therapy at weeks 24 and 48;
3. To assess the development level of drug resistance over 48 weeks of treatment;
4. To evaluate the metabolic and anthropometric parameters change over 48 weeks of treatment;
5. To evaluate the safety and tolerability of dual therapy (LPV/r+3TC).

Study Design

This is a non-interventional, product-focused, longitudinal and multi-center program with no control group.

Setting

For purpose of this program, participants were recruited and observed in 13 national and regional AIDS centers of the Russian Federation.

Subjects and Study Size, Including Dropouts

Patients were selected according to the following inclusion criteria:

- Age 18 years and older (male and female);
- HIV-1 infected patients on any triple HAART with plasma HIV-1 RNA level < 50 copies/mL for at least 6 months (two consequently plasma HIV-1 RNA levels) transferred as medically appropriate to LPV/r+3TC as decided by the physician in the routine clinical settings, or HIV-1 infected patients who were switched on the dual therapy (LPV/r+3TC) no more than 60 days prior to enrolment;
- Cumulative HAART experience at least 6 months;
- Authorization (Consent) for Use/Disclosure of Data signed by the patient.

Patients were not eligible for the current study if he/she:

- Had contraindications for the treatment with LPV/r and 3TC;
- Previously participated in this program.

In total, 216 patients were enrolled in the study. Out of them, 202 patients completed study per protocol, one patient (P15_452-05002) out of 202 who completed the study had no data on HIV-1 RNA level at Visit 5 (Week 48). 14 patients discontinued the study prematurely (2 left for the ineffectiveness of the therapy (HIV-1 RNA >50 copies/ml with confirmation in about one month), 4 withdrew their consent, 5 were lost to follow-up and 3 left because of pregnancy. See Table 2 (as added below after the basic disposition table).

Variables and Data Sources

Primary Variable

Proportion of patients on dual therapy (LPV/r+3TC) with undetectable HIV-1 RNA level at week 48 of the observational period.

Secondary Endpoints

1. Proportion of patients on dual therapy (LPV/r+3TC) with undetectable HIV-1 RNA level at week 24 of the observational period;
2. Absolute values of HIV-1 RNA viral loader at weeks 24 and 48 and the change as compared to the baseline (untransformed and base-10 logarithm transformed data);
3. Absolute values of CD4+ T-cell counts at weeks 24 and 48 and the change as compared to the baseline;
4. Proportion of patients who develop resistance to each class of drugs in the study regimen;
5. Absolute values at weeks 24 and 48 and changes of anthropometric measurements (arm, hip and waist circumference in cm) as compared to the baseline;
6. Absolute values at weeks 24 and 48 and changes of metabolic parameters (glucose, insulin, total cholesterol, LDL- and HDL-cholesterol, triglycerides, creatinine, ALT, AST) as compared to the baseline;
7. Proportion of patients with AEs (non-serious AEs, SAEs (including SAEs that cause deaths and AEs causing treatment discontinuations), with AEs organized according to System Organ Classification (SOCs) and by frequency.

Data Sources

Data for the study were collected within clinical interview with the patient and source documents at the center, including original documents, data and records.

Results and Discussion

The study was conducted at 13 clinical sites in the Russian Federation since November 18, 2015. The study was completed 27 May 2017 (last visit of the last patient). A total of 216 patients (72 Caucasian males (33.3 %) and 144 females (66.7 %)) were enrolled in this study, aged from 20 to 69 years old (Table 3). All participants were antiretroviral treatment-experienced with pre-suppressed plasma HIV-1 RNA level (undetectable with a <50 HIV RNA copies/mL threshold). Out of them, 14 patients

(5.36%) discontinued the study prematurely due to various reasons (4 patients withdrew their consent, 5 were lost to follow-up, 3 left because of pregnancy and for 2 patients ineffectiveness of the therapy was registered. For each of these 2 patients at Visit 2 HIV-1 RNA viral load ≥50 copies/mL was detected by the test and then confirmed by re-test one month later. Full breakdown of subject attrition during the study is given in Table 2. The remaining 202 patients completed this observational study, with one patient not having a final HIV-1 RNA viral load measurement. The results obtained for the final analysis endpoints imply that the LPV/r+3TC has an overall high virological efficacy and favourable safety profile for the patients. Thus, all patients that have data from HIV-1 RNA test at Visit 5 / Week 48 (201 of 201 patients; 100 %) demonstrated undetectable HIV-1 RNA level compared to 205 of 209 patients (98.1 %) at Visit 2 (12 weeks), 202 of 203 patients (99.5 %) at Visit 3 (Week 24) and 204 of 204 patients (100 %) at the Visit 4 (Week 36). For 2 of 209 patients (0.96%) at Visit 2 HIV-1 RNA viral load ≥50 copies/mL was detected by the test and then confirmed by re-test one month later (registered as infectiveness of the therapy, see Table 2 for the details). No discontinuations attributed to drug safety or intolerance were registered.

All participants were switched to dual therapy (LPV/r+3TC) on Day 0. Dual therapy was prescribed to the participants by the physician according to medical need under usual and customary practice of physician prescription and according to the approved market label (400mg/100 mg LPV/r B.I.D and 150mg 3TC BID).

Out of 216 enrolled patients 7 patients left study before Visit 2 (Week 12) because of withdrawal of consent, lost to follow-up, or pregnancy. Out of 209 patients that continued study 4 patients left before Visit 3 (Week 24), one patient withdrew consent, one left due to the pregnancy and for 2 patients at Visit 2 ineffectiveness of therapy was noted (HIV-1 RNA viral load ≥50 copies/mL was detected by the test and then confirmed by re-test). One patient before Visit 4 (Week 36) and 2 patients before Visit

5 (Week 48) lost to follow-up, so 202 patients completed study by protocol. Details of the study discontinuation by subjects are presented in Table 2.

All patients (n = 216, 100%) had undetectable HIV-1 RNA levels at enrollment. At the Visit 2 (Week 12), 205 of 209 patients (98.1 %) demonstrated undetectable HIV-1 RNA levels (<50 copies/mL) [95% CI: 95.17–99.48]. At the Visit 3 (Week 24), 202 of 203 patients (99.5 %) were virologically suppressed [95% CI: 97.29–99.99]. At the Visit 3 (Week 24) 2 patients out of 205 had no data on HIV-1 RNA viral load. At the Visit 4 (Week 36), 204 of 204 patients (100 %) demonstrated undetectable HIV-1 RNA levels [95% CI: 98.21–100.0]. At the Visit 5 (Week 48), 201 of 201 patients (100 %) were virologically suppressed [95% CI: 98.18–100]. One patient (P15_452-[redacted]) out of 202 who completed the study had no data on HIV-1 RNA level at Visit 5 (Week 48), but had data on viral load at other visits.

There was an increase in the mean viral load level at week 12 as compared to the baseline, estimated as 82.25 ± 1133.852 copies/mL [95% CI: 0.00–236.87] (untransformed data) and 0.06 ± 0.525 copies/mL [95% CI: 0.00–0.13] (log_{10}-transformed data), which was not statistically significant. The absolute values of the HIV-1 RNA viral load declined to near to baseline levels at week 24. At the weeks 36 and 48 no increase above baseline value (<50 copies/mL) HIV-1 RNA viral load was observed. The increase in the mean HIV-1 RNA viral load of ≥ 50 copies/mL at Visit 2 (week 12) was attributable to 4 patients with the mean viral load of 4322.50±8061.201 copies/mL at Visit 2, all other patients at this time point remained undetectable. One patient at Visit 3 (Week 24) was observed to have a viral load of 70 copies/mL). One patient out of 4 demonstrated NNRTI/NRTI resistance and was diagnosed with numerous mutations at Visit 2 (Week 12). The individual viral loads for these individuals are tabulated in Table 9. Observed NNRTI resistance-related mutations in detectable patients included K103N/S/H/T/R/Q/E, V106A/M/I, Y188L/C/H/F and G190A/S/E/Q/C/T/V. NRTI resistance in the said patient was

defined by L74V/I, V75T/M/A/S, K65R/N/E, M184V/I and Q151M complex mutations.

There was a statistically significant increase in the absolute and relative CD4+T-lymphocyte cell counts at weeks 24 and 48 in comparison to the baseline. The absolute CD4+T-lymphocyte values increased in average by 64.70± 165.06 cells/mm^3 [95% CI: 41.97–87.43] at week 24 and 111.75± 184.477 cells/mm^3 [95% CI: 86.15–137.34] at week 48. The mean relative change was 0.96±4.879% [95% CI: 0.28–1.63] at week 24 and 1.43 ± 6.314% [95% CI: 0.55–2.31] at week 48.

No significant changes from baseline of anthropometric parameters were observed in patients on dual therapy at weeks 24 and 48. No clinically significant abnormalities of anthropometric parameters were registered in the study.

No significant changes from baseline were found for the means of the laboratory parameters at weeks 24 and 48, except for a slight increase of ALT mean values (in the group that included 16 patients from one site, the increase was registered for 5 patients, all of them had co-infection by Hepatitis C virus). One patient (0.5%) had a clinically significant abnormality of the ALT level at week 24. One patient (0.5%) had clinically significant abnormality of glucose level at week 48. For 2 patients (1%) at week 24 and 2 patients (1.0%) at week 48 clinically significant abnormalities of total cholesterol level were registered. No other clinically significant abnormalities of metabolic parameters were registered in the study.

In the study, 3 patients (1.4%) reported 9 adverse events. No Serious Adverse Events were reported throughout the study. Most of the Adverse Events registered were gastrointestinal disorders (two patients reported 6 Adverse Events).

CI values obtained for each endpoint estimation parameters indicate the studied therapy regimen as virologically effective and with a favourable safety profile. These outcomes are consistent with clinical trial studies switching virologically suppressed

patients for LPV/r plus 3TC dual therapy indicating favourable efficacy and safety profiles translate from a clinical trial setting [9] to the real world setting in the Russian Federation.

Marketing Authorization Holder(s)

AbbVie LLC, [redacted]

Names and Affiliations of Principal Investigators

A full list of Principal Investigators is provided in the in Section 3.0 of the report.