

1.0 Abstract

Title

Multi-Center Observational Study to Assess Effectiveness and Safety of Fixed Dose Combination of Generic Product of Lopinavir/ritonavir in HIV-1 Infected Patients after Switching from Kaletra® (Lopinavir/ritonavir) for administrative reasons in the Routine Clinical Settings of Russian Federation (COPI)

Keywords

Lopinavir/ritonavir, generic, HIV-1

Rationale and Background

Kaletra® is the brand name of a coformulation of two antiretroviral agents: lopinavir and ritonavir (LPV/r), indicated in combination with other antiretroviral agents for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infection. Lopinavir is a potent inhibitor of the HIV-1 protease, which is needed for production of mature virus [1]. It blocks maturation of HIV-1 and therefore its infectivity.

Kaletra® has a well-established efficacy and safety profile confirmed in clinical trials and in real clinical setting worldwide [2,3,4]. It was originally registered in Russia in 2008 [5]. Currently the regimen is included in the country essential drug list and is widely used within the national HIV treatment program. In 2017 a generic version of LPV/r – “Kalidavir®” obtained registration certificate in Russia [6]. According to the country legislation, the sole bioequivalence data is sufficient for a generic product to obtain marketing authorization while clinical trials data are not required. There is a limited experience of Kalidavir® usage in Russia and to date there are no publicly available data on effectiveness and safety of this generic product neither in clinical trials nor in real word setting. However, clinical characteristics of Kalidavir® such as virologic efficacy and tolerability are critically important for healthcare practitioners and patients.

Research Question

Is switching from a brand name of LPV/r (Kaletra) to a generic formulation of LPV/r (Kalidavir) associated with negative clinical outcomes (e.g., loss of viral suppression, increased adverse events) in HIV-1 infected patients?

Primary Objective

To describe the effectiveness and safety of generic LPV/r over a 48-week treatment period in a population of treatment-experienced HIV-1 infected patients with two last tests with an undetectable plasma HIV-1 RNA level within the last 24 weeks before switching and previously treated with Kaletra® on a continuous basis during 48 weeks before switching in the routine clinical settings of Russian Federation.

Secondary Objectives

1. To describe reasons for switching from generic LPV/r.
2. To describe drug resistance over 48 weeks of treatment with a generic LPV/r.

Study Design

This is a mixed prospective-retrospective, multi-center observational study to assess the virologic effectiveness of generic product of LPV/r.

Study Setting

Study population

HIV-1 infected patients that were switched from Kaletra® (LPV/r) for administrative reasons were recruited and observed in 10 national and regional AIDS centers. Patient visits and health care reflected the routine clinical practice.

Inclusion Criteria

1. Age 18 years and older (male and female).
2. HIV-1 infected patients on any dual or triple HAART with Kaletra® under observation at least 48 weeks and with two consequent plasma HIV-1 RNA levels within the last 24 weeks <50 copies/mL switched to a generic LPV/r as decided by the physician in the routine clinical settings within last 24 weeks from study enrollment date.
3. HIV-1 infected patients with last available CD4+ T-cell count test result > 200 cells/mm³ before switching before initiating generic LPV/r.
4. Other (not LPV/r) HAART medicine components of dual or triple HAART not planned to change after switching to generic product of LPV/r.

5. Signed Inform Consent form by patient

Exclusion Criteria

1. Has contraindications for the treatment with LPV/r.
2. Legal or physical incapability of patient to sign Inform Consent form

Study Duration

Start of data collection in the study was on 01 November 2019 and it was planned to observe prospectively or retrospectively (in case of available data) it about 48 weeks after switching from Kaletra®. However, the study was terminated 8 June 2020.

Study Size

A sample size of 239 patients based on binominal distribution and an exact Clopper-Pearson confidence interval with lower and upper limits 0.243 and 0.362 (12% confidence width ($\pm 6\%$ half of width)) was sufficient to provide statistically stable estimates of descriptive study objectives and variables. It was assumed that co-primary effectiveness and safety endpoints are whether or not failure over 48 weeks, respectively and that the proportion of failure after switching to fixed dose combination of generic product of lopinavir/ritonavir is 30% for both primary endpoints.

Data Sources

Data for the study was collected from a clinical interview of patient with consulting/treating physician and from source documents at the center. Source documents was original documents, data and records.

Primary Endpoints

There were two co-primary endpoints: one primary endpoint for effectiveness and one primary endpoint for safety. The effectiveness primary endpoint was the proportion of patients who meet at least one of the following composite endpoint criteria, assessed at each visit over 48 weeks of observational period in patients treated with a fixed dose combination of generic product of lopinavir/ritonavir:

- a. HIV-1- RNA viral load >50 copies/ml, OR

- b. CD4+ T-cell counts < 200 cells/mm³.

The safety primary endpoint was the proportion of patients who meet at least one of the following composite endpoint criteria, assessed at each visit over 48 weeks of observational period in patients treated with a fixed dose combination of generic product of lopinavir/ritonavir:

- a. development of new or recurrent opportunistic infections or HIV-associated malignancies (based on physician observation and decision), OR
- b. any Serious Adverse Event (SAE), associated with HIV treatment.

Secondary Endpoints

- Untransformed (absolute) and base-10 logarithm transformed data values of HIV-1- RNA viral load at weeks 12, 24, 36 and 48 and the change as compared to the last measure on Kaletra® treatment (untransformed and base-10 logarithm transformed data).
- Absolute values of CD4+ T-cell counts at weeks 12, 24, 36 and 48 and the change as compared to the last measure on Kaletra® treatment.
- Proportion of patients with reasons for switching from generic LPV/r to other ART for HIV therapy or change in the dosing regimen – medical reason (ineffectiveness, intolerance/toxicity, other), non-medical reasons (lack of availability of generic LPV/r, other) and other reasons.
- Proportion of patients who develop HIV drug resistance over 48 weeks of generic LPV/r treatment.
- Proportions of patients with AEs (non-serious AEs [including AE causing treatment discontinuations], SAEs, [including SAEs that cause deaths]) over Kaletra® and generic LPV/r treatment periods.

Results

Patients' disposition

239 patients were enrolled in the study from 01.11.2019 to 21.01.2020 and included in the statistical analysis. One patient had premature discontinuation due to intolerability of therapy in the group treated by generic LPV/r.

Demographic and clinical characteristics

Among 239 patients 77 (32.2%) were males and 162 (67.8%) females. The mean age was 39.2 (SD 7.11). Anthropometric characteristics such as height (in cm), weight (in kg) and BMI (in kg/m²) constituted 169.2 (SD 8.86), 67.2 (SD 13.44) and 23.32 (SD 3.46) accordingly.

The median duration of HIV-infection in months was 120.66 (Q1 64.49; Q3 171.17). Mode of HIV transmission distributed as following: heterosexual contact - 188 (78.7%), intravenous drug user - 55 (23.0%), men having sex with men - 5 (2.1%) and NA/unknown - 1 (0.4%).

Prior liver disorders had 19 (7.9%) patients. Among them, 19 (7.9%) patients had chronic hepatitis C, one (0.4%) patient had hepatic echinococcosis, one (0.4%) patient had cytomegalovirus chorioretinitis and one (0.4%) patient had disseminated tuberculosis in the previous medical history.

Overall, 73 (30.5%) had concomitant liver disorders. Among them, 63 (26.4%) were diagnosed with chronic hepatitis C, 11 (4.6%) with chronic hepatitis B, 1 (0.4%) with acute hepatitis C, 5 (2.1%) with hepatic fibrosis, 3 (1.3%) with hepatic cirrhosis, 1 (0.4%) with chronic hepatitis, 1 (0.4%) with gallbladder polyp and 1 (0.4%) with haemangioma of liver. Prior AIDS-defining illnesses were observed in 47 (19.7%) patients. Thirty-two (13.4%) patients had current AIDS-defining illnesses. Prior chronic kidney disease was observed in 2 (0.8%) cases. Current kidney disease was diagnosed in 9 (3.8%) patients. Concomitant metabolism and nutrition disorders were in 4 (1.7%) cases. Thirty-two (13.4%) patients had drug dependence, 2 (0.8%) drug use disorder and 1 (0.4%) was drug abuser in the medical history. One patient 1 (0.4%) had concomitant encephalopathy and one patient 1 (0.4%) had concomitant alcoholism. Twenty (8.4%) had medical history with other prior disorders and 52 (21.8%) had other concomitant disorders. 20 (8.4%) patients had concomitant medications.

Effectiveness evaluation

Over the 12-weeks treatment period with generic LPV/r the failure on either effectiveness or safety primary endpoints occurred in 15 (6.3% (CI 3.6%; 10.1%)) cases. Fourteen patients (5.9% (CI 3.2%; 6.9%)) failed to achieve the primary effectiveness endpoint, while 1 patient (0.4% (CI 0.0%; 2.3%)) failed to achieve the primary safety endpoint. Eleven (4.6% (CI 2.3%; 8.1%)) patients had HIV-1 RNA > 50 copies/mL and 3 patients (1.3% (CI 0.3%; 3.6%)) had CD4+ T-lymphocyte count < 200 cells/mm³ over 12 weeks treatment with generic LPV/r. Serious adverse event associated with HIV treatment were observed in one case 1 (0.4% (CI 0.0%; 2.3%)).

Safety Evaluation

In 48 weeks of retrospective period of treatment with Kaletra only 1 (0.4%) patient had 2 AEs - nausea and decreased appetite.

Over 12 weeks of treatment with generic LPV/r, 6 (2.5% (CI 0.9%; 5.4%)) patients had 10 AEs (6 non-serious and 4 serious). Among these AEs were 2 (0.8%) weight decreased, 1 (0.4%) loss of consciousness, 1 (0.4%) presyncope, 1 (0.4%) diarrhea, 1 (0.4%) vomiting, 1 (0.4%) anaemia, 1 (0.4%) tricuspid valve disease, 1 (0.4%) tricuspid valve incompetence and 1 (0.4%) endocarditis.

5 (2.1%) patients had non-serious adverse events such as weight decrease, presyncope, diarrhea, vomiting, anaemia. 1 (0.4%) had serious adverse events were loss of consciousness (it was related to study drug SAE), tricuspid valve disease, tricuspid valve incompetence and endocarditis. 1 (0.4%) patient had adverse events leading to study drug discontinuation were weight decrease, loss of consciousness and diarrhea.

Marketing Authorisation Holder

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