
1.0 Abstract

Title

Use of KALETRA in combination with new substances in adult HIV-infected patients:
Data from the German multicenter PROTEKT cohort

Keywords

HIV, lopinavir/ritonavir, LPV/r, PROTEKT

Rationale and Background

PROTEKT is a non-interventional cohort study including ART-naïve and treatment-experienced HIV-1-infected patients receiving cART including LPV/r plus an antiretroviral drug not of the NRTI class, i.e., an integrase inhibitor (INI), a chemokine receptor type 5 (CCR5) antagonist, or second-generation NNRTI. There were no restrictions concerning additional antiretrovirals. Assignment of a patient to a particular cART was part of routine clinical care and was independent from the conduct of PROTEKT. Ethics approval was obtained prior to initiation of the study.

Research Question and Objectives

The goal of this study was to observe and collect data on the usage, dosing, tolerability, and efficacy of KALETRA® tablets in combination with other new agents. The primary objective was the evaluation of tolerability when using lopinavir/ritonavir in combination with an INI, a CCR5 antagonist, or a second-generation NNRTI. Other objectives included immunologic responses (i.e., the change in CD4 T-cell count), the characterization of baseline resistance and the development of resistance, virologic outcomes and the durability of the LPV/r-based regimens.

Study Design

Retro- and prospective, multicenter, observational, non-interventional cohort study.

Setting

Routine clinical practice in Germany

Subjects and Study Size, Including Dropouts:

The study population consisted of ART-naïve and treatment-experienced HIV-infected patients initiated on new LPV/r-based combination regimens. By the end of the recruitment phase, 501 patients were included, 82% of them were treatment-experienced.

Variables and Data Sources

The electronic case report forms included demographic data, HIV-related variables such as the time since first HIV diagnosis, HIV subtype, variables of past and current antiretroviral therapy, reasons for switch to new cART, reasons for discontinuation as well as efficacy and safety laboratory parameters (HIV RNA, CD4 cell count, serum chemistry parameters). Clinical variables included height, weight, comorbidities and the prevalence of specific (laboratory) adverse events (AEs; including WHO grades) at the time of the patients' visits. Only data available in the patient files which were assessed during the usual clinical management of patients were documented. The study protocol did not mandate visits or laboratory measurements beyond those performed in clinical routine. All patient data entered in the electronic case report form were pseudonymised.

Results

The full analysis set consisted of 501 adult patients, 86% of male gender and 85% Caucasians. Median age was 45 years. Of patients with available information, HIV-1 subtype B was most prevalent (86%). Most common concomitant diseases were HIV-associated disease (26%), followed by chronic hepatitis C (11%) and renal disease (7%). The majority of the patients (82%) were ART-experienced, 48% with PIs (21% with one, 27% with at least two PIs); 18% of the patients (90/501) were ART-naïve prior to initiation of LPV/r-based cART. Main reasons for switch to the new regimen in ART-experienced

patients were adverse events (25%), therapy failure (24%) and drug resistance (13%). In 86% of the patients, the new agent combined with LPV/r was raltegravir (55% receiving dual therapy); 12.6% received maraviroc; etravirine or dolutegravir were used in $\leq 1.0\%$ of patients.

In total, 8% of the study population had a baseline HIV RNA level $> 100,000$ copies/mL (68% of ART-naïve and 7% of ART-experienced patients). Of ART-experienced patients, almost half of the patients were on suppressive ART at study entry (45%). Median baseline CD4 cell count was $396/\mu\text{L}$ ($302/\mu\text{L}$ in ART-naïve and $\geq 400/\mu\text{L}$ in the ART-experienced subgroups).

Resistance testing prior to switch to new cART was available in nearly one third of patients (159/501; 32%); 17 (11%) patients harbored resistance or partial resistance to protease inhibitors; in 4 of them susceptibility of LPV/r was affected; NRTI and NNRTI susceptibility was affected in 40% and 29% of patients, respectively. Of 108 tropism test results prior to baseline, 34 showed the presence of CXCR4 tropic virus. Genotypic resistance testing during follow-up was available in 6 patients, one of them showing LPV/r-associated resistance mutations which were already present at baseline.

The (restricted) mean time to discontinuation was 176 weeks. In ART-naïve patients, the mean time to discontinuation was shorter than in ART-experienced patients (ART-naïve 113 weeks, PI-naïve 174 weeks, PI-experienced (1 PI) 147 weeks, PI-experienced (> 1 PI) 164 weeks; $P < 0.001$ for comparison across all treatment groups). At Week 144, 62% of the total cohort were still on LPV/r-based cART, 8% were lost to follow-up; 30% of patients discontinued LPV/r-based cART prior to Week 144. Main reasons for discontinuation were adverse events (in 12% of the total cohort), patient's wish (5%), virologic failure (4%) and therapy simplification (4%).

In ART-naïve patients, the median CD4 cell changes from baseline were $+200/\mu\text{L}$, $+309/\mu\text{L}$ and $+286/\mu\text{L}$ at Weeks 48, 96 and 144. In ART-experienced patients (either PI-naïve,

PI-experienced with one PI or with more than one PI), the median CD4 cell increases at Weeks 48, 96 and 144 range between 54 – 77/ μ L, 82 – 120/ μ L and 116 – 152/ μ L, respectively.

Intend-to-treat (ITT) analyses for virologic outcomes at Week 48 were as follows: 51% of ART-naïve, 71% of PI-naïve, 68% of PI-experienced (1 PI) and 77% of PI-experienced (> 1 PI) patients had an HIV-1 RNA level < 50 copies/mL. As-treated (AT) analyses showed the following virologic success rates: 67% in ART-naïve patients, 86% in PI-naïve patients, 73% in PI-experienced (1 PI) patients and 87% in PI-experienced (> 1 PI) patients.

Of documented adverse events specified in the eCRF, the most common events at baseline were hypercholesterolemia (2.6%), diarrhea (2.4%) and hypertriglyceridemia (1.4%). There were no new findings concerning the safety of LPV/r-based cART. Regarding the whole study period from Week 0 to Week 144, the most common adverse events (> 5%) documented at least once per patient were diarrhea (at least one episode in 27.3% of patients), hypercholesterolemia (17.8%), hypertriglyceridemia (14.8%), mood disorder (9.8%), nausea (8.6%), elevated γ GT (7.8%), abdominal pain (7.8%), high LDL cholesterol (7.2%) and elevated ALT/SGPT (6.4%).

Discussion

The use of new LPV/r-based combination regimens, in particular LPV/r + RAL as dual therapy or part of cART showed a good persistence with still two thirds of patients remaining on the specific combinations for more than 144 weeks (Kaplan-Meier estimates). Depending on pre-treatment status, between 51% and 77% of patients showed viral suppression to levels < 50 HIV_RNA copies/mL (ITT) after 48 weeks. Evaluation of adverse events did not reveal new findings concerning the safety of LPV/r-based cART. Antiretroviral LPV/r-based combinations other than the classical NRTI-based triple regimens offer an alternative approach for treatment initiation in specific situations as well as for treatment switch in antiretroviral experienced patients.

Marketing Authorisation Holder(s)

AbbVie Ltd. (formerly Abbott)

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