Safety and Effectiveness of Darunavir in Korean Patients with Human Immunodeficiency Virus 1 Infection: A Post-Marketing Observational Study

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ABSTRACT

We aimed to evaluate the safety and effectiveness of darunavir (DRV) in the treatment of human immunodeficiency virus-1 (HIV-1) infection in Korea. From October 29, 2010, 225 eligible patients with HIV-1 infection receiving DRV were enrolled. DRV was administered with other antiretroviral agents, and followed for 24 weeks. The primary objective was safety evaluation, and effectiveness was assessed by viral load and CD4 T cell counts after 12 weeks and 24 weeks. Adverse drug reactions occurred in 18 patients (9.2%); diarrhea was the most common. Viral load was controlled (<400 copies/mL) in 90.9% of patients. CD4 T cell counts were increased 45.0/mm³ significantly at Week 12 (P = 0.0002), and 70.5/mm³ at Week 24 (P <0.0001). DRV safety and effectiveness was consistent with previous studies.

Keywords: Darunavir; Safety; Observational study; Human immunodeficiency virus-1; Korea

INTRODUCTION

Darunavir (DRV) is a protease inhibitor (PI) and approved antiretroviral agent for the treatment of human immunodeficiency virus 1 (HIV-1) infection. DRV is indicated for various patient subgroups, from treatment naïve to treatment experienced [1-4]. Co-administration of DRV with low-dose ritonavir is called boosted DRV. For initial antiretroviral therapy (ART), combining boosted DRV and other antiretrovirals (ARVs) is currently recommended [5]. The safety and effectiveness of boosted DRV has been confirmed in several post-marketing clinical studies [6-9]. However, it is unclear whether the same profiles exist in the Korean population. Therefore, we aimed to confirm the overall safety and effectiveness of boosted DRV-based ART in Korea.

MATERIALS AND METHODS

This was an observational, non-interventional, prospective, multicenter study to evaluate DRV safety and effectiveness from October 29, 2010 to October 28, 2016. Twenty one hospitals in Korea participated in this study. The study was approved by local ethics committees of...
Darunavir for the management of HIV-1 in Korea

Author Contributions
Conceptualization: JK. Data curation: YK. Formal analysis: YK. Methodology: HK, YK, JK. Project administration: HK, YK, JK. Validation: YK. Visualization: HK, YK. Writing - original draft: HK, YK. Writing - review & editing: HK, YK, JK.

Each center and conducted in accordance with the Declaration of Helsinki, and this study is conducted in compliance with Korean regulations, as post-marketing surveillance (PMS).

Inclusion criteria were age ≥19 years, HIV-1 infection, and treatment with DRV (PREZISTA®, 400 mg tablet), regardless of treatment history. Exclusion criteria were off-label use of DRV or ritonavir (e.g., without ritonavir).

DRV 800 mg with ritonavir 100 mg once daily was administered orally along with ARVs selected by the investigator, considering treatment guidelines and patient conditions.

After consent to provide data, individual patient's information were collected during 24 weeks of observation period; demographics, medical history, prior and concomitant medications, DRV treatment, laboratory results of HIV-RNA viral load and CD4 T cell count, and adverse event.

Safety was assessed by compiling adverse event (AE) severity, outcomes, and causal relationships to DRV during treatment. Any medical signs, symptoms, or disease during the study were reported as AE by the investigator. Adverse drug reactions (ADRs) were AEs for which a causal relationship with DRV could not be ruled out by investigator's judgement. Effectiveness was assessed by measuring the viral load and CD4 T cell count at Week 12 and Week 24. Responders were patients with viral loads <400 copies/mL after each DRV treatment.

Statistical analyses were performed using SAS (SAS Institute Inc., Cary, NC, USA) as described in the local marketing authorization. Continuous data are presented as descriptive statistics, and categorical data are presented as frequencies and percentages. Paired t-tests were performed to compare the change in CD4 T cell count from baseline to post DRV treatment.

RESULTS

1. Demographics and baseline characteristics
A total 225 patients enrolled in the 21 hospitals nationwide. Of them, 30 patients were excluded from analysis (17 were off-label users; 13 violated the surveillance start dates) and finally 195 were included in the safety set. Of these, 155 patients were included in the effectiveness set (40 were excluded owing to a lack of viral load and CD4 T cell assessments) (Fig. 1).

Table 1 provides demographics and baseline characteristics of patients. All patients were Korean, and 92.3% of the patients were male. The median age was 45.0 years. The most common reason for discontinuation of prior antiretroviral therapy was intolerance in 39 patients (20.0%), followed by AEs in 35 patients (17.9%), virologic treatment failure in 9 patients (4.6%), and immunological treatment failure in 7 patients (3.6%).

2. Safety
All reported AEs and ADRs with incidence ≥1% are presented in Table 2. No DRV-related deaths occurred. Unexpected ADRs (not previously listed in local prescribing information) were reported in 8 patients; these included tinea pedis, alopecia, dermatitis, drug eruption, upper abdominal pain, hyperlipidemia, hypertension, and chest discomfort. No cardiovascular events were reported during the study period.
3. Effectiveness

Plasma HIV-RNA viral load results are shown in Fig. 2 and CD4 T cell count analysis is provided in Table 3. More than 90% (n = 90) of patients responded to DRV treatment, with 90.9% and 94.7% response rates 12 (N = 155) and 24 (N = 107) weeks after DRV treatment, respectively. The CD4 T-cell count was increased by 45.0 cells/mm³ from baseline to week 12 ($P = 0.0002$), and 70.5 cells/mm³ at week 24 ($P < 0.0001$). Treatment failure occurred in 1 patient, who displayed virologic failure after 107 days of DRV treatment.

DISCUSSION

Here, we evaluated the safety and effectiveness of DRV in Korea; this is the first large-scale study performed using post-marketing data. ARTs containing DRV/ritonavir were generally safe and well tolerated in patients infected with HIV-1. To date, no studies have reported safety findings dissimilar to our own.

With the development of new ARTs, HIV treatment guidelines changed significantly during the study period [5]. Although the combination of dual nucleoside reverse-transcriptase inhibitors (NRTIs) with integrase inhibitor (INSTI), which is currently available on the
market as a single fixed dose pill, is typically recommended, DRV-containing ART is also recommended for special populations owing to its good resistance profile. Further, DRV should be combined with ritonavir for combination ART-based HIV-1 treatment. However, combination therapies are typically limited by the increased number of pills, so concomitant use of DRV with ritonavir may have a problem of decreased adherence. However, since our study did not assess treatment compliance such as pill counting, it was not possible to evaluate the treatment compliance on combination of DRV with ritonavir. Nevertheless, our results demonstrate the successful control of the patients’ viral loads.

In previous results of PMS for lamivudine/abacavir in HIV-1 patients in Korea, suggested hypersensitivity, or allergic reactions such as diarrhea, nausea, rash, skin eruption, and hypertriglyceridemia have been reported, which is associated with abacavir’s HLA-B*5701 allele [10]. In this study, 30% of patients used abacavir as concomitant ART, and diarrhea, nausea,

| Table 1. Demographics and baseline characteristics |
|-----------------------------------------------|
|                                | n (% ) |
| Gender                         |        |
| Male                           | 180 (92.3) |
| Female                         | 15 (7.7) |
| Age Median (Min - Max)         | 45.0 (21 - 80) |
| Ethnicity                      |        |
| Asian (Korean)                 | 195 (100) |
| AIDS-defining disease          |        |
| Yes                            | 55 (28.2) |
| Pneumocystis jirovecii pneumonia | 19 (9.7) |
| Tuberculosis                   | 7 (3.6) |
| Candidiasis                    | 7 (3.6) |
| Cytomegalovirus disease        | 4 (2.1) |
| Hepatic impairment              |        |
| Yes                            | 9 (4.6) |
| Renal impairment               |        |
| Yes                            | 2 (1.0) |
| Previous ART                   |        |
| Yes                            | 101 (51.8) |
| Number of previous ART regimens|        |
| 1                              | 73 (37.4) |
| 2                              | 17 (8.7) |
| ≥3                             | 11 (5.6) |
| Reason for discontinuing previous ART |        |
| Intolerance                    | 39 (20.0) |
| Virologic treatment failure    | 9 (4.6) |
| Immunological treatment failure| 7 (3.6) |
| Adverse event                  | 35 (17.9) |
| Other                          | 38 (19.5) |
| Concomitant ARV                 |        |
| Yes                            | 195 (100.0) |
| Dual NRTIs                     | 184 (94.3) |
| TDF/FTC                        | 126 (64.6) |
| ABC/3TC                        | 57 (29.2) |
| AZT/3TC                        | 1 (0.5) |
| Single NRTI                    | 2 (1.0) |
| ABC                            | 1 (0.5) |
| TDF                            | 1 (0.5) |
| No NRTI                        | 9 (4.6) |
| Viral load (copies/mL)         |        |
| n = 175                        |        |
| Median (Min - Max)             | 20.0 (0 - 500,000) |
| <400                           | 118 (67.4) |
| ≥400                           | 57 (32.6) |
| CD4 T cells/mm³                |        |
| n = 183                        |        |
| Median (Min - Max)             | 379.0 (6 - 1,355) |

*Hepatic impairment includes past history or current comorbidities of aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, liver abscess, hepatic cirrhosis, hepatocellular carcinoma, alcoholic hepatitis, autoimmune hepatitis.

*Renal impairment includes past history or current comorbidities of chronic kidney disease.

*Raltegravir (5), none of concomitant ARV except DRV/ritonavir (3), etravirine (1).

AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy, ARV, antiretrovirals; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; ABC, abacavir; 3TC, lamivudine; AZT, azidothymidine; NRTI, nucleoside reverse-transcriptase inhibitor; n’, number of patients with available results; CD4, cluster of differentiation 4.
rash, and hyperglyceridemia were reported as treatment-related adverse reactions. However, it was not collected whether these adverse reactions were related to darunavir or due to combined abacavir, but there is no significant safety concern since the regimen of ART follows the treatment guideline which is known to be tolerated in HIV-1 patients.

As ART is lifelong, confirming its long-term safety is crucial. Our study included not only newly initiated DRV patients, but also patients who had previously used DRV before the study. Therefore, it is expected to be safe even in the long-term used patients’ group. However, it

Table 2. Adverse events with incidence ≥1%

| Adverse Events                  | Adverse Drug Reactions |
|---------------------------------|------------------------|
| Overall                         | n (%)                  | n (%)                  |
| Gastrointestinal disorders      | 71 (36.4)              | 18 (9.2)               |
| Diarrhea                        | 10 (5.1)               | 3 (1.5)                |
| Nausea                          | 3 (1.5)                | 2 (1.0)                |
| Chronic Gastritis               | 2 (1.0)                | 0 (0.0)                |
| Abdominal Pain                  | 2 (1.0)                | 0 (0.0)                |
| Gastritis                       | 2 (1.0)                | 0 (0.0)                |
| Skin and subcutaneous tissue disorders |                   |
| Rash                            | 5 (2.6)                | 2 (1.0)                |
| Pruritus                        | 3 (1.5)                | 0 (0.0)                |
| Urticaria                       | 3 (1.5)                | 0 (0.0)                |
| Alopecia                        | 3 (1.5)                | 1 (0.5)                |
| Dermatitis                      | 2 (1.0)                | 1 (0.5)                |
| Infections and infestations     |                        |                       |
| Herpes zoster                   | 4 (2.1)                | 0 (0.0)                |
| Tinea pedis                     | 3 (1.5)                | 1 (0.5)                |
| Nasopharyngitis                 | 2 (1.0)                | 0 (0.0)                |
| Pneumonia                       | 2 (1.0)                | 0 (0.0)                |
| Nervous system disorders        |                        |                       |
| Headache                        | 8 (4.3)                | 1 (0.5)                |
| Dizziness                       | 2 (1.0)                | 0 (0.0)                |
| Respiratory, thoracic, and mediastinal Disorders |         |
| Cough                           | 6 (3.1)                | 0 (0.0)                |
| Allergic rhinitis               | 3 (1.5)                | 0 (0.0)                |
| Metabolism and nutrition disorders |                      |
| Decreased appetite              | 4 (2.1)                | 0 (0.0)                |
| Hypertriglyceridemia            | 2 (1.0)                | 2 (1.0)                |
| Hypokalemia                     | 2 (1.0)                | 0 (0.0)                |
| Musculoskeletal and connective tissue disorders |         |
| Arthralgia                      | 2 (1.0)                | 1 (0.5)                |
| Back Pain                       | 2 (1.0)                | 0 (0.0)                |
| Investigations                  |                        |                       |
| Increased blood triglycerides   | 2 (1.0)                | 0 (0.0)                |
| Blood and lymphatic system disorders |                |
| Neutropenia                     | 2 (1.0)                | 0 (0.0)                |
| Vascular disorders              |                        |                       |
| Hypertension                    | 2 (1.0)                | 1 (0.5)                |

Table 3. Effectiveness results

| Visit       | Statistics | Value | Baseline | Change         |
|-------------|------------|-------|----------|----------------|
| Week 12 (n = 103) | Median     | 407.0 | 363.0    | 45.0           |
|             | Min - Max  | 70 - 2,384 | 6 - 1,298 | -389 - 1,086  |
|             | P-value    | -     | -        | 0.0002         |
| Week 24 (n = 98)   | Median     | 492.0 | 419.5    | 70.5           |
|             | Min - Max  | 117 - 1,883 | 17 - 1,248 | -589 - 823    |
|             | P-value    | -     | -        | <0.0001        |

n' = number of patients with available results.

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is still difficult to confirm long-term safety with this data alone, the further data of longer follow-up period is required to observe sufficiently for long-term safety.

It is known that PIs cause abnormalities in lipid pathways so hypertriglyceridemia or hyperlipidemia could be occurred when patients treated with PIs. There were 1% of hypertriglyceridemia reported in our study, whereas the cumulative incidence of new-onset of hypertriglyceridemia was 19% in the Israel cohort study which is higher incidence than our result [11]. However since the Israel cohort study has covered all PIs, it is difficult to compare our results directly. And there may be differences between race, however it is needed further research to confirm this difference.

And previous findings reported that PIs are associated with increased risk of cardiovascular events related to metabolic abnormalities such as dyslipidemia or insulin resistance [12]. However, despite the correction of dyslipidemia, patients treated with ritonavir-boosted DRV have a 60% greater risk of adverse cardiovascular events [13] and cardiovascular disease are not considered as a risk of DRV by reviewing comprehensive data from clinical trials, post-marketing, and epidemiologic [14]. So further studies on the unique mechanism of DRV compared to that of other PIs are needed.

The effectiveness of DRV was evaluated based on viral suppression and immune activation, as determined by calculating viral load and CD4 T-cell. In this study, most of patients achieved viral suppression and CD4 T-cell count was significantly increased. Compared to another results of abacavir PMS conducted in a similar environment, the mean CD4 T-cell count was 533.7/mm³ and 439.9/mm³, respectively after 24 weeks of treatment [10, 15], which was similar to the mean CD4 T-cell count of 530.1/mm³ in this study. Therefore, DRV can be expected to have a similar immune activation effect as other ARTs.

This post-marketing surveillance demonstrated that DRV has favorable safety and effectiveness profiles in patients with HIV-1 infection in Korea.

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