Infect Chemother. 2021 Sep;53(3):539-545
https://doi.org/10.3947/ic.2020.0124
pISSN 2093-2340·eISSN 2092-6448

Infection & Chemotherapy

Brief Communication

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

Hyeongyeong Kim, Youngdoe Kim, and Jiho Kang

Medical affairs, Janssen Korea Ltd., Seoul, Korea

Received: Apr 28, 2021
Accepted: Jun 15, 2021

Corresponding Author:
Jiho Kang, MD, MPH
Medical affairs, Janssen Korea Ltd., 92 Hangang-daero, Yongsan-gu, Seoul 04386, Korea.
Tel: +82-2-2094-4801
Fax: +82-2-3452-8085
E-mail: jkang45@its.jnj.com

ORCID iDs
Hyeongyeong Kim
https://orcid.org/0000-0003-2752-7358
Youngdoe Kim
https://orcid.org/0000-0002-0772-6360
Jiho Kang
https://orcid.org/0000-0002-8208-2243

Funding
This study was supported by Janssen Korea Ltd.

Conflict of Interest
All authors are employees of Janssen Korea Ltd.

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/mm^3 significantly at Week 12 (P = 0.0002), and 70.5/mm^3 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

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.

https://doi.org/10.3947/ic.2020.0124

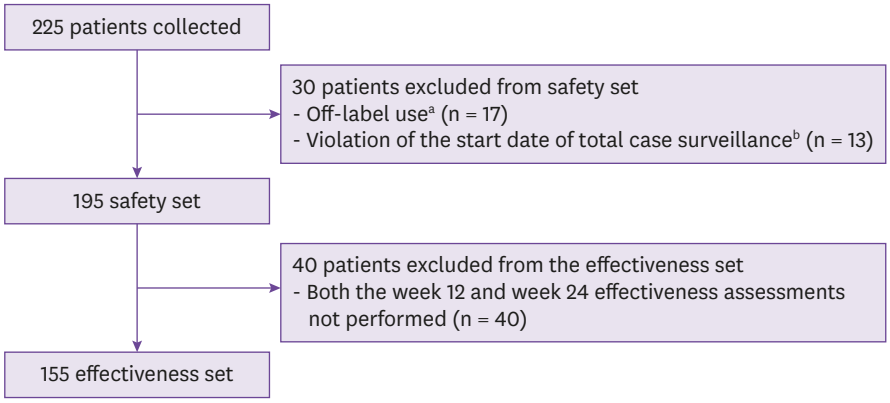

Figure 1. Disposition of patients.
[a]Prohibited drug used (n = 15), essential concomitant medication ritonavir not used (n = 2).
[b]Use of PREZISTA® before the enrollment date prior to the PMS protocol amendment to a total case surveillance.

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/mm^3 from baseline to week 12 (P = 0.0002), and 70.5 cells/mm^3 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

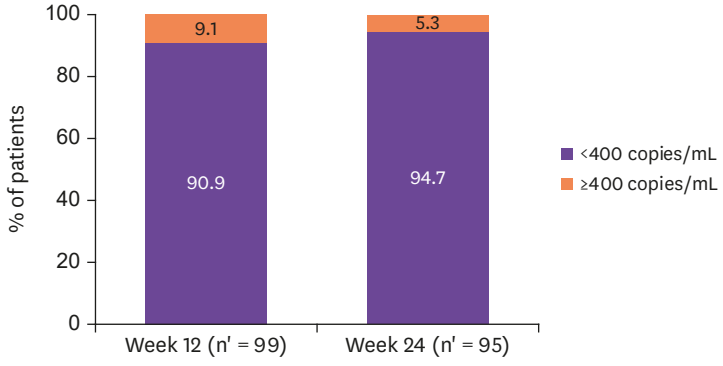

Figure 2. HIV-RNA viral load.
n′= number of patients with available results.
HIV, human immunodeficiency virus.

https://doi.org/10.3947/ic.2020.0124

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[a]	Yes	9 (4.6)
Renal impairment[b]	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[c]	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/mm^3	*n'* = 183	
	Median (Min - Max)	379.0 (6 - 1,355)

[a]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.
[b]Renal impairment includes past history or current comorbidities of chronic kidney disease.
[c]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.

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,

https://doi.org/10.3947/ic.2020.0124

Table 2. Adverse events with incidence ≥1%

	Adverse Events	Adverse Drug Reactions
	n (%)	n (%)
Overall	71 (36.4)	18 (9.2)
Gastrointestinal disorders		
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 (4.1)	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.

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

https://doi.org/10.3947/ic.2020.0124

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/mm^3 and 439.9/mm^3, respectively after 24 weeks of treatment [10, 15], which was similar to the mean CD4 T-cell count of 530.1/mm^3 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.

REFERENCES

1. Bánhegyi D, Katlama C, da Cunha CA, Schneider S, Rachlis A, Workman C, De Meyer S, Vandevoorde A, Van De Casteele T, Tomaka F. Week 96 efficacy, virology and safety of darunavir/r versus lopinavir/r in treatment-experienced patients in TITAN. Curr HIV Res 2012;10:171-81.
PUBMED | CROSSREF
2. Madruga JV, Berger D, McMurchie M, Suter F, Banhegyi D, Ruxrungtham K, Norris D, Lefebvre E, de Béthune MP, Tomaka F, De Pauw M, Vangeneugden T, Spinosa-Guzman S; TITAN study group. Efficacy and safety of darunavir-ritonavir compared with that of lopinavir-ritonavir at 48 weeks in treatment-experienced, HIV-infected patients in TITAN: a randomised controlled phase III trial. Lancet 2007;370:49-58.
PUBMED | CROSSREF
3. Mills AM, Nelson M, Jayaweera D, Ruxrungtham K, Cassetti I, Girard PM, Workman C, Dierynck I, Sekar V, Abeele CV, Lavreys L. Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis. AIDS 2009;23:1679-88.
PUBMED | CROSSREF
4. Orkin C, DeJesus E, Khanlou H, Stoehr A, Supparatpinyo K, Lathouwers E, Lefebvre E, Opsomer M, Van de Casteele T, Tomaka F. Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1-infected treatment-naïve patients in the ARTEMIS trial. HIV Med 2013;14:49-59.
PUBMED | CROSSREF

5. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/ AdultandAdolescentGL.pdf. Accessed 23 July 2021.
6. Willig JH, Aban I, Nevin CR, Ye J, Raper JL, McKinnel JA, Delaitsch LL, Mrus JM, De La Rosa GR, Mugavero MJ, Saag MS. Darunavir outcomes study: comparative effectiveness of virologic suppression, regimen durability, and discontinuation reasons for three-class experienced patients at 48 weeks. AIDS Res Hum Retroviruses 2010;26:1279-85.
PUBMED | CROSSREF
7. Benea OE, Streinu-Cercel A, Dorobăț C, Rugină S, Negruțiu L, Cupșa A, Duiculescu D, Chiriac C, Itu C, Prisăcariu LJ, Iosif I. Efficacy and safety of darunavir (Prezista(®)) with low-dose ritonavir and other antiretroviral medications in subtype F HIV-1 infected, treatment-experienced subjects in Romania: a post-authorization, open-label, one-cohort, non-interventional, prospective study. Germs 2014;4:59-69.
PUBMED | CROSSREF
8. Podzamczer D, Imaz A, Perez I, Viciana P, Valencia E, Curto J, Martín T, Castaño M, Rojas J, Espinosa N, Moreno V, Asensi V, Iribarren JA, Clotet B, Force L, Bachiller P, Knobel H, López Bernaldo De Quirós JC, Blanco JR, Rozas N, Vergas J, Ocampo A, Camacho A, Flores J, Gomez-Sirvent JL; KIDAR Study Group. Abacavir/lamivudine plus darunavir/ritonavir in routine clinical practice: a multicentre experience in antiretroviral therapy-naive and -experienced patients. J Antimicrob Chemother 2014;69:2536-40.
PUBMED | CROSSREF
9. Antinori A, Meraviglia P, Monforte A, Castagna A, Mussini C, Bini T, Gianotti N, Rusconi S, Colella E, Airoldi G, Mancusi D, Termini R. Effectiveness, durability, and safety of darunavir/ritonavir in HIV-1-infected patients in routine clinical practice in Italy: a postauthorization noninterventional study. Drug Des Devel Ther 2016;10:1589-603.
PUBMED
10. Ann H, Lee YS, Kim YS, Jung SI, Lee SH, Lee CS, Lee JS, Choi WS, Choi YH, Kim SW. Safety and effectiveness analysis of Kivexa® (lamivudine/abacavir sulfate) in human immunodeficiency virus infected Korean patients. Infect Chemother 2019;51:150-60.
PUBMED | CROSSREF
11. Tsiodras S, Mantzoros C, Hammer S, Samore M. Effects of protease inhibitors on hyperglycemia, hyperlipidemia, and lipodystrophy: a 5-year cohort study. Arch Intern Med 2000;160:2050-6.
PUBMED | CROSSREF
12. Baker JV, Sharma S, Achhra AC, Bernardino JI, Bogner JR, Duprez D, Emery S, Gazzard B, Gordin J, Grandits G, Phillips AN, Schwarze S, Soliman EZ, Spector SA, Tambussi G, Lundgren J; INSIGHT (International Network for Strategic Initiatives in Global HIV Trials) START (Strategic Timing of Antiretroviral Treatment) Study Group. Changes in cardiovascular disease risk factors with immediate versus deferred antiretroviral therapy initiation among HIV-positive participants in the START (Strategic Timing of Antiretroviral Treatment) trial. J Am Heart Assoc 2017;6:e004987.
PUBMED | CROSSREF
13. Ryom L, Lundgren JD, El-Sadr W, Reiss P, Kirk O, Law M, Phillips A, Weber R, Fontas E, d' Arminio Monforte A, De Wit S, Dabis F, Hatleberg CI, Sabin C, Mocroft A; D:A:D study group. Cardiovascular disease and use of contemporary protease inhibitors: the D:A:D international prospective multicohort study. Lancet HIV 2018;5:e291-300.
PUBMED | CROSSREF
14. Opsomer M, Dimitrova D, Verspeelt J, Purrington A, Mehbob A, Chavers S, Pai H, Vanveggel S, Luo D, Brown K, Moecklinghoff C, Nettles RE, Boven K. Correction to: Evaluation of cardiovascular disease risk in HIV-1-infected patients treated with darunavir. Drugs R D 2018;18:249-50.
PUBMED | CROSSREF
15. Ann H, Kim KH, Choi HY, Chang HH, Han SH, Kim KH, Lee JS, Kim YS, Park KH, Kim YK, Sohn JW, Yun NR, Lee CS, Choi YW, Lee YS, Kim SW. Safety and efficacy of Ziagen (Abacavir Sulfate) in HIV-infected Korean patients. Infect Chemother 2017;49:205-12.
PUBMED | CROSSREF