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Safety and Efficacy of Ziagen (Abacavir Sulfate) in HIV-Infected Korean Patients

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Background: Abacavir is a widely-used nucleoside reverse transcriptase inhibitor for the treatment of human immunodeficiency virus (HIV) infection. Mandatory postmarketing surveillance was conducted in Korea to monitor the safety and evaluate the effectiveness of Ziagen® (abacavir sulfate 300 mg; ViiV Healthcare, Middlesex, UK).

Materials and Methods: An open-label, multi-center, non-interventional postmarketing surveillance study was conducted from June 2010 to June 2016 to monitor the safety and effectiveness of Ziagen across 12 hospitals in Korea. Subjects older than 18 years taking Ziagen according to prescribing information were enrolled. The primary outcome was defined as the occurrence of any adverse events after Ziagen administration. Secondary outcomes included the occurrence of adverse drug reactions, occurrence of serious adverse events, and effectiveness of Ziagen administration.

Results: A total of 669 patients were enrolled in this study, with a total observation period of 1047.8 person-years. Of these, 90.7% of patients were male. The mean age of patients was 45.8±11.9 years. One-hundred ninety-six (29.3%) patients reported 315 adverse events, and four patients reported seven serious adverse events, without any fatal events. There was one potential case of an abacavir hypersensitivity reaction. Among the 97 adverse drug reactions that were reported from 75 patients, the most frequent adverse drug reactions included diarrhea (12 events), dyspepsia (10 events), and rash (9 events). No ischemic heart disease was observed. In the effectiveness analysis, 91% of patients achieved HIV-1 RNA under 50 copies/mL after 24 months of observation with abacavir administration.

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Conclusion: Our data showed the safety and effectiveness of Ziagen in a real-world setting. During the study period, Ziagen was well-tolerated, with one incident of a clinically suspected abacavir hypersensitivity reaction. The postmarketing surveillance of Ziagen did not highlight any new safety information. These data may be helpful in understanding abacavir and the HIV treatment practices in Korea.

Key Words: Abacavir; Human immunodeficiency virus; Drug-related side effects and adverse reactions; Pharmacoepidemiology

Introduction

Abacavir is a nucleoside reverse transcriptase inhibitor (NRTI) used for the treatment of human immunodeficiency virus (HIV) infection. In combination with other antiretroviral agents, abacavir has proven antiretroviral efficacy, which is attributable to its ability to reduce HIV-1 replication and improve immunologic parameters [1-4]. Abacavir is one of the first-line recommendations among NRTIs in many international treatment guidelines [5-7]. It can cause hypersensitivity reactions, especially in patients who are positive for the *HLA-B*5701* allele, and the association of abacavir and ischemic heart disease remains inconclusive based on available data [8-12]. Ziagen®(abacavir sulfate 300 mg; ViiV Healthcare, Middlesex, UK) was first approved in Korea in 2001 as an orphan drug and later became available on the market in 2010. We carried out a postmarketing surveillance study to evaluate the safety and effectiveness of Ziagen in a real-world setting.

Materials and Methods

1. Study design and population

An open-label, multi-center, non-interventional postmarketing surveillance study was conducted from June 2010 to June 2016 to monitor the safety and effectiveness of Ziagen across 12 hospitals in Korea. Patients with confirmed HIV infection taking Ziagen according to prescribing information were included. Subjects who started Ziagen before the study period were also included, and the observation started on the day consent was obtained. Patients with contraindications for abacavir described in the prescribing information, such as moderate to severe hepatic impairment (Child-Pugh class B or C), end-stage renal diseases (estimated glomerular filtration rate ≤15 mL/min/1.73 m^2 or those receiving renal replacement treatments), or confirmed *HLA-B*5701* carriers, were excluded. The primary outcome was defined as the occurrence of any adverse events (AEs) following Ziagen administration. Secondary outcomes included the occurrence of unexpected adverse drug reactions (ADRs), occurrence of serious adverse events (SAEs), and the effectiveness of Ziagen administration. Effectiveness was assessed via measurement of changes in plasma HIV-1 RNA viral load and CD4+ T-cell counts for each participant during the study period. Regarding the non-interventional study design, a subjective assessment of *clinical improvement* was also included for the subjects whose observation period on the study was over 24 weeks. A total of 780 subjects were planned to be enrolled, with an estimated 20% drop out rate, in order to provide 600 evaluable subjects for the primary analysis. This study was approved by the Institutional Review Board of each participating hospitals.

2. Definitions

Based on WHO-ART 092, an AE was defined as any untoward medical occurrence in a subject temporarily associated with the use of Ziagen, whether or not considered related to the medicinal product. An SAE was defined as any untoward medical occurrence at any dose that (1) results in death, (2) is life-threatening, (3) requires inpatient hospitalization or prolongation of existing hospitalization, (4) results in persistent or significant disability/incapacity, or (5) results in a congenital anomaly/birth defect. An ADR was defined as all noxious and unintended responses related to Ziagen. Physicians classified the relatedness of the event to the drug into 6 categories (certain, probable/likely, possible, unlikely, conditional/unclassified, and unassessable/unclassifiable) by WHO-UMC causality categories [13]. If the causality between Ziagen and AEs is considered certain, probable/likely, possible, conditional/unclassified, or unassessable/unclassifiable, the AEs were classified as ADRs. ADRs that are not listed in the Korean prescribing information were classified as unexpected ADRs.

3. Demographic and clinical data

Physician visits were scheduled in accordance with each

physician's routine practice. At the initial visit, demographic information (including subject's sex, age, height, body weight, and pregnancy status); medical history (including allergy history, renal impairment, hepatic impairment, other concomitant diseases, treatment duration of Ziagen, time since HIV diagnosis, and HIV treatment history); concomitant medications; laboratory values (including viral load); and CD4+ T-cell counts were recorded. Physicians were guided to record any treatment-emergent AEs during the follow-up visits. Results of all HIV-1 RNA viral loads and CD4+ T-cell counts performed within the study period were collected. At the final study visit, the effectiveness of Ziagen was subjectively evaluated as improved, no change, worsened, or not assessed based on the investigator's medical judgment.

4. Statistical analysis

Continuous variables were expressed as the mean ± one standard deviation, and discrete variables were expressed as the frequency and rate. Once all AEs were classified by preferred terms and system-organ classes, the frequency and percentage of each AE were calculated. Because of the non-interventional design of the study, not all subjects had their HIV-1 RNA viral loads and CD4+ T-cell counts evaluated every 3 months. Test results without an exact date and invalid test results were excluded from the analysis. The available values were collected for each 3-month time frame, and the ratio of participants with HIV-1 RNA <50 copies/mL and mean CD4+ T-cell counts were calculated. Statistical calculation was carried out using SAS version 9.0 (SAS Institute Inc, Cary, NC, USA).

Results

1. Characteristics of study participants

Data were collected from 671 patients; however, due to 2 cases of protocol deviation, 669 patients were included in safety analysis. The total observation period was 1047.8 person-years. The majority (90.7%) of included patients were male. The mean age of patients was 45.8 ± 11.9 years. Patients older than 65 years and those diagnosed with HIV infection within the past year represented 6.9% and 16.4% of the population, respectively. The majority of patients (63.8%) took abacavir with another NRTI plus a boosted protease inhibitor (PI). Patients with concomitant diseases represented 70.3% of the population; eight patients had renal impairment (chronic kidney disease stage 2 to 3 [14]); 43 patients had hepatic impairment (Child-Pugh class A score; Table 1).

2. Safety and tolerability

One-hundred ninety-six patients reported 315 adverse events. The incidence of diarrhea (23/669, 3.4%) was the highest, followed by that of dyspepsia (19/669, 2.8%), dizziness (18/669, 2.7%), pharyngitis (15/669, 2.2%), and rash (14/669, 2.1%).

Four patients reported SAEs. A 72-year-old man presented with nausea, vomiting, fever, and lethargy after 54 days of Ziagen administration. His symptoms resolved within 24 hours of stopping Ziagen use. *HLA-B*5701* allele status was not available. The investigator reported that this case may possibly be

Table 1. Baseline characteristics of the subjects included in safety analysis

Total, n (%)	**669 (100)**
Male gender, n (%)	607 (90.7)
Age, mean (SD), y	45.8 (11.9)
18-64, n (%), y	623 (93.1)
65-80, n (%), y	46 (6.9)
BMI, mean (SD), kg/m^2	22.3 (2.9)
Time since HIV diagnosis, mean (SD), y	4.4 (4.0)
Less than 1 year, n (%)	110 (16.4)
2-5 years, n (%)	267 (39.9)
6-10 years, n (%)	216 (32.3)
Over 10 years, n (%)	61 (9.1)
Duration of Ziagen administration observation, n (%)[a]	
Less than 3 months	120 (17.9)
4-12 months	424 (63.4)
Over 12 months	125 (18.7)
ART regimen at study registration, n (%)	
Ziagen + 1 NRTI + NNRTI	145 (21.7)
Ziagen + 1 NRTI + PI	427 (63.8)
Ziagen + 1 NRTI + INI	49 (7.3)
Others	50 (7.5)
History of any allergy, n (%)	12 (1.8)
Any concomitant diseases, n (%)	470 (70.3)
Renal impairment	8 (1.2)
Hepatic impairment	43 (6.4)
Cardiovascular diseases	101 (21.5)
Concomitant drug use, n (%)	
Antihypertensive drugs	92 (13.8)
Glucose-lowering drugs including insulin	39 (5.8)
Lipid-lowering drugs	99 (14.8)

[a]Subjects who started Ziagen before the study period were also included; the observation began on the day of consent.
SD, standard deviation; BMI, body mass index; ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INI, integrase inhibitor

an abacavir hypersensitivity reaction. Other presentations of cellulitis, abscess formation, and general weakness were determined to not be associated with use of the study drug (Table 2).

Seventy-five patients reported 97 ADRs. Diarrhea was the most common ADR (12/669, 1.8%), followed by that of dyspepsia (10/669, 1.5%), rash (9/669, 1.3%), nausea (7/669, 1.0%), and dizziness (5/669, 0.7%; Table 3).

In addition to the one possible case of abacavir hypersensitivity reaction, no further cases of abacavir hypersensitivity reaction were reported in this study. No cases of ischemic heart disease were reported.

3. Effectiveness

The proportion of patients who achieved HIV-1 RNA <50 copies/mL increased over time during Ziagen treatment (Fig. 1). A total of 669 patients had initial HIV-1 RNA viral loads. Initially, 44.6% of patients had viral loads below 50 copies/mL; but, after 24 months of abacavir administration, 90.8% of the 76 patients who had a 24-month HIV-1 RNA blood test achieved HIV-1 RNA under 50 copies/mL. In addition, the mean CD4+ T-cell count increased from 334.7 cells/mm^3 at baseline to 577.6 cells/mm^3 after 24 months of abacavir treatment (Fig. 2). Excluding 158 subjects whose observation duration was less than 24 weeks, 511 of the 669 patients were eligible for the subjective effectiveness analysis. Three-hundred sixty-nine patients (72.2%) were rated as *improved*, 30 (5.9%) were rated as *unchanged*; 5 (1.0%) were rated as *worsened*; and 107 (21%) were *non-assessed*.

Discussion

This was a postmarketing surveillance study of 669 patients in Korea designed to observe the safety and effectiveness of Ziagen.

A 3-drug regimen with a 2-NRTI backbone plus one core agent (non-nucleoside reverse transcriptase inhibitor [NNRTI], PI, integrase inhibitor [INI]) has become the standard treatment of HIV infection. Abacavir is one of the most commonly used NRTI backbones, which is recommended in major international treatment guidelines in combination with dolutegravir and lamivudine [6, 7, 15]. Abacavir is also available as a fixed-dose combination as abacavir/lamivudine and dolutegravir/abacavir/lamivudine.

A total of 669 patients were included in the 6-year postmarketing surveillance study. Due to the introduction of the abacavir/lamivudine fixed-dose combination in 2012 in Korea, recruitment of subjects has been slow since 2014. Most patients were recruited between 2011 and 2013. Male patients accounted for 90.7% of the total study population, reflecting a male-dominant sex ratio in Korea [16, 17]. In terms of the antiretroviral therapy regimen (Table 1), 63.8% of patients used abacavir with another NRTI and a PI. In comparison with other NNRTI dominance in other Asian countries during the study period, our data reflect the popular use of PI-based regimens in Korea [18, 19]. Since INIs were only introduced in 2010, a small portion of patients was taking an INI with abacavir in Korea. Although we set *HLA-B*5701* carrier status as an exclusion criterion, *HLA-B*5701* allele status was unknown in all subjects.

Although generally well tolerated, there have been reports of AEs related to abacavir [1, 20]. In this study, there were four SAEs; however, none of the SAEs were *certain* or *probable/likely* linked to the use of Ziagen by investigator assessment. There was one patient (Case 1 in Table 2) presenting with nausea, vomiting, fever, and lethargy on the 54th day of abacavir administration whose condition improved within 24 hours of drug cessation. This case is a clinically suspected abacavir hypersensitivity reaction based on the presenting symptoms and time of resolution after abacavir cessation. Abacavir hypersensitivity may occur in 5% to 8% of patients and requires careful attention, as it can be life threatening without appropriate management [21, 22]. Abacavir hypersensitivity is strongly associated with the *HLA-B*5701* allele; thus, genotypic screening

Table 2. Clinical characteristics of cases with serious adverse events

	Age	Gender	Adverse event	Treatment duration	Outcome	Drug cessation	Association with Ziagen
1	72	M	Nausea, vomiting, fever, lethargy	54 days	Resolved	Yes	Possible
2	80	M	Foot cellulitis	209 days	Resolved	No	Unlikely
3	44	M	Liver abscess	282 days	Resolved	No	Unlikely
4	40	M	General weakness	7 days	Resolved	No	Unassessable

M, male.

Table 3. Frequency and expectedness of adverse drug reactions

	Number	Incidence, %	Listed[a]
Gastrointestinal			
Diarrhea	12	1.8	Yes
Dyspepsia	10	1.5	Yes
Nausea	7	1.0	Yes
Abdominal pain	2	0.3	Yes
Vomit	4	0.6	Yes
Oral ulcer	1	0.1	Yes
Respiratory tract			
Pharyngitis	1	0.1	Yes
Cough	1	0.1	Yes
Increased sputum	1	0.1	No
Skin and appendages			
Rash	9	1.3	Yes
Pruritus	4	0.6	No
Urticaria	2	0.3	Yes
Increased sweating	1	0.1	No
Skin nodules	1	0.1	No
Dermatitis	1	0.1	No
Nervous system			
Dizziness	5	0.7	Yes
Numbness	1	0.1	Yes
Systemic disorders			
Fever	2	0.3	Yes
Worsened general condition	1	0.1	No
Fatigue	1	0.1	Yes
Generalized ache	2	0.3	Yes
Flush	1	0.1	No
Chills	1	0.1	Yes
Weakness	1	0.1	Yes
Edema	1	0.1	Yes
Psychiatric disorder			
Sleep disorder	2	0.3	Yes
Loss of appetite	4	0.6	Yes
Lethargy	1	0.1	Yes
Bad dreams	1	0.1	Yes
Metabolic disorder			
Hypertriglyceridemia	4	0.6	Yes
Hyperlipidemia	1	0.1	Yes
Hypercholesterolemia	1	0.1	Yes
Dyslipidemia, Unspecified	1	0.1	Yes
Hepatobiliary system			
Hyperbilirubinemia	2	0.3	Yes
Elevated ALT	3	0.4	Yes
Elevated AST	3	0.4	Yes
Jaundice	1	0.1	Yes
Total	97 events (75 patients)		

[a]AEs listed in Korean prescribing information.
ALT, alanine transaminase; AST, aspartate transaminase; AE, adverse event.

is recommended before the use of abacavir-containing products [8, 23-25]. Research reporting the incidence of *HLA-B*5701* varies considerably by ethnicity, and its prevalence can be as low as 0.3% to 0.5% in Korea [26-28]. A report showed no *HLA-B*5701*-positive HIV-infected patients in a study of 534 Korean subjects (95% confidence interval [CI], 0.00-0.69) [28]. This report raised a question about the cost-effectiveness of *HLA-B*5701* testing versus careful patient monitoring for abacavir hypersensitivity reactions after prescribing abacavir in regions with a very low incidence of the *HLA-B*5701* allele. In our study, the incidence of abacavir hypersensitivity was 0.09 (95% CI, 0.0048-0.4700) per 100 person-years of follow-up.

Although the risk of ischemic heart disease and the use of abacavir were not associated in several recent meta-analyses [10, 11], the overall evidence is inconclusive [9, 12]. In the present study, no patients using abacavir had evidence of ischemic heart disease. Similarly, no abacavir-related cardiovascular events were observed in the postmarketing surveillance study

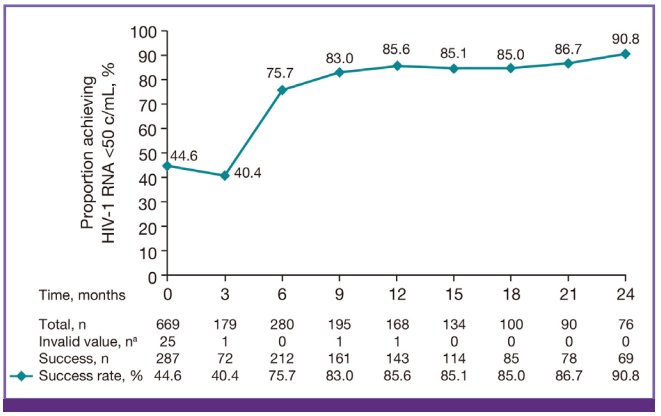

Figure 1. Proportion achieving HIV-1 RNA <50 copies/mL.
[a]Missing test date or unknown test results.

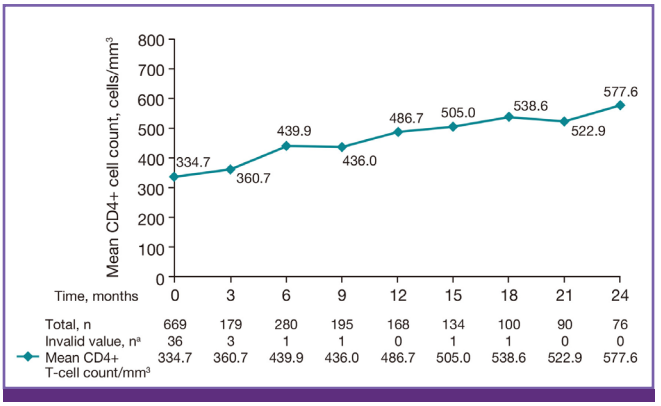

Figure 2. Changes in CD4+ T-cell counts.
[a]Missing test date or unknown test results.

of abacavir and abacavir/lamivudine in Japan [20, 29].

The incidences of ADRs were considerably low in our study. The most frequent ADRs reported were gastrointestinal (GI) disturbance, including diarrhea (12 cases, 1.8%), dyspepsia (10 cases, 1.5%), and nausea (7 cases, 1.0%). It is difficult to identify abacavir-specific AEs, since abacavir was used in combination with other medications including antiretroviral drugs and other concomitant drugs. It is interesting to note the low incidence of GI AEs, despite the high proportion of subjects (63.8%) taking boosted PI–based regimens in Korea, which is lower than the 10% reported incidence of GI disturbance in the postmarketing surveillance report in Japan [20]. The lower incidence of GI-related AEs in Korea may require further investigation.

In the effectiveness analysis, we assessed the proportion of patients achieving plasma HIV-1 RNA <50 copies/mL. There were 44.6% of 669 patients with suppressed viral load at the start of study. After 24 months of an abacavir-containing treatment regimen, 90.8% out of 76 patients who had HIV-1 RNA results at 24 months achieved plasma HIV-1 RNA under 50 copies/mL. The mean CD4+ T-cell count increased from 334.7 cells/mm^3 at baseline to 577.6 cell/mm^3 after 24 months of an abacavir-containing treatment regimen. Without a well-controlled comparator arm, it is hard to evaluate the effectiveness of abacavir as a single agent; however, we could observe a numerically positive virologic and immunologic effect of abacavir-containing antiretroviral therapy from this study.

This study has several limitations. Firstly, it is a postmarketing surveillance study with limited variables. We could not collect actual laboratory results such as serum creatinine and liver enzymes. Secondly, due to the observational study design, interventions for study participants, including prescheduled blood test intervals, were not allowed; the data were inconsistent with regard to the duration of abacavir use or specific intervals of individual viral load testing. Lastly, the study does not include a comparator arm; thus, it is hard to directly attribute the positive effectiveness data solely to the antiviral activity of abacavir. These data may provide supportive information to healthcare practitioners, as our study results reflect positive real-world data of HIV treatment using an abacavir-containing regimen.

In conclusion, we report in a postmarketing surveillance study the real-world data from 669 patients using abacavir. Abacavir was generally well tolerated. The incidence of abacavir hypersensitivity was rare. Cardiovascular AEs were not reported with the use of abacavir in this study. More patients achieved plasma HIV-1 RNA <50 copies/mL with abacavir administration than baseline, and the CD4+ T-cell count was increased from baseline. These results may be helpful for understanding abacavir use and HIV treatment patterns in Korea. We are collecting further safety and effectiveness information for abacavir from spontaneous reports and postmarketing surveillance of other drugs containing abacavir.

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Conflicts of Interest

No conflicts of interest.

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