INTERNAL MEDICINE

□ CASE REPORT □

An HIV-infected Pregnant Woman Treated with the Long-term Administration of Antiretroviral Therapy Including Raltegravir

Kenichiro Yaita[1], Shigeru Inoue[2], Takashi Horinouchi[2], Masahiro Kinoshita[3], Mitsuaki Unno[3], Osuke Iwata[3], Yuhei Tanaka[3], Kenji Gotoh[3], Mikio Ishibashi[4], Yoshiro Sakai[1,4], Kenji Masunaga[1], Hiroshi Watanabe[1] and Masaki Tominaga[5]

Abstract

A 27-year-old HIV-infected pregnant Japanese woman was admitted to our hospital at gestational week 14. The patient's HIV viral load was 71,000 copies/mL, and her CD4 cell count was 147 cells/mm^3. Zidovudine, lamivudine, and lopinavir/ritonavir were administered at gestational week 18. Because the viral load increased to 222,000 copies/mL at the initiation of antiretroviral therapy, we added raltegravir. The decrease in the viral load was satisfactory, and a caesarean delivery was performed. Although the plasma concentration of raltegravir in the neonate was significantly high (2,482 ng/mL), no adverse event was confirmed. There was no evidence of the mother-to-child transmission of HIV.

Key words: raltegravir, integrase strand transfer inhibitor, plasma concentration, HIV, pregnancy

(Intern Med 55: 2727-2730, 2016)
(DOI: 10.2169/internalmedicine.55.6653)

Introduction

In Japan, approximately 30-50 pregnant women are diagnosed with an attendant HIV infection annually (1). Most of these patients were diagnosed as HIV-positive before becoming pregnant and received antiretroviral therapy (ART) (1). In the Japanese manual for HIV-infected pregnancy (1), the regimen includes a ritonavir (rtv)-boosted protease inhibitor [lopinavir (LPV)], zidovudine (AZT) and lamivudine (3TC) are preferred; however, the speed of the virological suppression by these drugs might be insufficient in special situations such as late gestation (2).

Raltegravir (RAL) is the first integrase strand transfer inhibitor (INSTI) and is known to have a strong effect in decreasing the viral load (VL) (3). In Japan, some foreigners have been diagnosed in late gestation and have been administered ART that includes RAL (4, 5); however, there have been no published report of Japanese pregnant women receiving ART that includes RAL. In addition, the plasma concentrations of RAL in the mother and child have not been studied in Japan. We herein report the safety and efficacy of long-term RAL administration for pregnant women according to the findings of a case report and review of the literature.

Case Report

A 27-year-old pregnant Japanese woman, gravida 2, para 0, was admitted to our hospital at gestational week 14 in 2014 because of HIV infection. She had a past medical history of Fitz-Hugh-Curtis syndrome. Her body weight was 64.5 kg. The VL on admission was 71,000 copies/mL, and the CD4 cell count was 147 cells/mm^3 (the VL was also

[1]Department of Infection Control and Prevention, Kurume University School of Medicine, Japan, [2]Department of Obstetrics and Gynecology, Kurume University School of Medicine, Japan, [3]Department of Pediatrics and Child Health, Kurume University School of Medicine, Japan, [4]Department of Pharmacy, Kurume University Hospital, Japan and [5]Department of Medicine, Division of Respirology, Neurology, and Rheumatology, Kurume University School of Medicine, Japan
Received for publication October 5, 2015; Accepted for publication December 22, 2015
Correspondence to Dr. Kenichiro Yaita, kyaita81@gmail.com

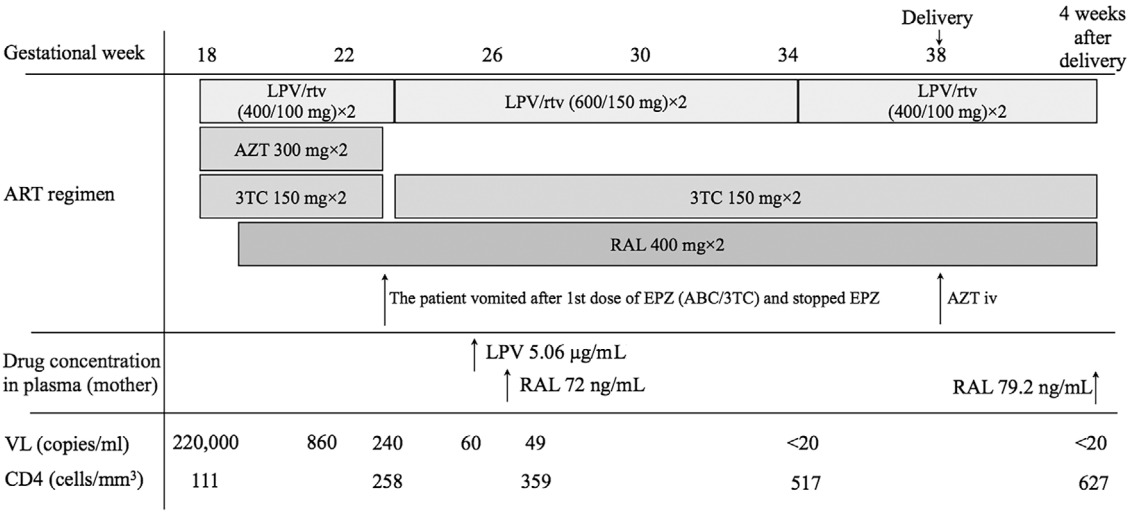

Figure. Clinical course. ABC: abacavir, ART: antiretroviral therapy, AZT: zidovudine, EPZ: EPZICOM®, iv: intravenous infusion, LPV: lopinavir, RAL: raltegravir, rtv: ritonavir, VL: viral load, 3TC: lamivudine

measured by a physician in another clinic and the value was 71,000 copies/mL in gestational week 12). No major mutation associated with drug resistance was detected. There was no evidence of an opportunistic infection or liver/renal functional disorder. During the initial evaluation, there were no special events with the exception of an allergy (a rash and fever) to sulfamethoxazole-trimethoprim (ST), thus we changed ST to atovaquone for the prophylaxis of pneumocystis pneumonia. At gestational week 18, the standard ART during pregnancy recommended by the Japanese manual for the prevention of the mother-to-child transmission of HIV (LPV/rtv 400/100 mg twice daily, AZT 300 mg twice daily and 3TC 150 mg twice daily) (1) was administered; however, the VL and CD4 cell counts at the initiation of ART were 222,000 copies/mL and 111 cells/mm^3, respectively. One week after the start of ART, RAL (400 mg twice daily) was added to the initial regimen. Because there was only 20 weeks until the expected date of confinement, and due to the possibility of premature birth, we expected the efficacy of RAL to provide a more rapid virological suppression than that of LPV/rtv (3, 6). The VL was decreased to 860 copies/mL at gestational week 21. We additionally changed AZT/3TC to abacavir (ABC)/3TC (600/300 mg once daily), which is marketed as EPZICOM® (EPZ), due to decreases in her hemoglobin level from 9.2 g/dL to 8.2 g/dL at gestational week 23. However, because an adverse event of vomiting occurred 5 hours after the first dose, we immediately stopped EPZ. After 5 days of stopping EPZ, we increased the dose of LPV/rtv to 600/150 mg twice daily due to the possibility of insufficient plasma concentrations of LPV in late pregnancy (7) and added 3TC again. Her ART regimen finally settled at 3TC/LPV/rtv/RAL. In order to confirm the efficacy of ART during pregnancy, we evaluated the trough plasma concentrations of the drugs, LPV at gestational week 25 and RAL at gestational week 26, and the results were 5.06 μg/mL and 72 ng/mL, respectively. According to these results, we reduced the dose of LPV/rtv to 800/200 mg at gestational week 34. At this point, the VL was suppressed to less than 20 copies/mL.

A caesarean delivery was performed at gestational week 38, with the administration of AZT infusion during delivery without complications. Because a small number of cases are reported in Japan, the Japanese manual recommends AZT infusion for all patients to insure that the mother-to-child transmission of HIV is prevented (1). The body weight of the infant was 2,662 g, with Apgar scores of 8/9. The infant was prescribed AZT syrup for four weeks. Breastfeeding was avoided. There was no evidence of the mother-to-child transmission of HIV at 1 and 4 months. In addition, the infant's plasma concentration of RAL was evaluated 1.5 hours after delivery (6 hours after the mother's last dose of RAL), and the result was 2,482 ng/mL. The plasma concentration of RAL decreased to less than 10 ng/mL at 53 days after birth. The mother's clinical course, including the plasma concentrations of the drugs, is detailed in Figure.

Discussion

RAL is the first INSTI (approved in the U.S. by 2007 and in Japan by 2008) to demonstrate a strong efficacy for a rapid reduction of the VL (3). Recently, new INSTIs such as elvitegravir and dolutegravir have come onto the market; however, RAL remains among the first-line regimens in the guideline for ART (8).

RAL is a relatively venerable INSTI, although the experience of using INSTIs for pregnant women is limited. We searched the PubMed, Google Scholar and Ichushi (the Japanese database for medical literature and conference proceedings) databases for RAL-prescribed pregnancy case reports and clinical studies written in the English and Japanese languages, and identified 138 cases, including two non-Japanese case reports from Japan (4, 5, 9-28). In the litera-

Table. The Relationship of Plasma Concentration of RAL between Mothers and Infants.

Reference	(12)	(12)	(12)	(13)	(13)	(13)	Our case
Case No.	1	2	3	1	2	3	-
Race	Rwandan	Ghanaian	Ugandan	Ugandan	Ghanaian	Zimbabwean	Japanese
Collection time of mother's samples							
after delivery (hours)	0	1	0	3	1	9	-
after maternal dose of RAL (hours)	6	3	10.5	7	13	12	-
Plasma concentration of RAL in mother (ng/mL)	2,318	64	300	493	22	50	72*
Collection time of infant's samples							
after delivery (hours)	1	2	0.5	3	1	2.5	1.5
after maternal dose of RAL (hours)	7	4	11	7	13	5.5	6
Plasma concentration of RAL in infant (ng/mL)	3,781	120	602	3,634	209	776	2,482
Infant/mother plasma concentration ratio of RAL	1.63	1.88	2	7.37	9.5	15.52	34.5

RAL: raltegravir
* Our case's trough plasma concentration of RAL was checked in second trimester.

ture review, the VL before the start of RAL varied from a non-detectable level to 17,400,000 copies/mL, and most of the patients (at least 100 patients, 72%) were administered RAL in the third trimester (late pregnancy). The duration of RAL use also varied from just 14 hours to the entire maternal period. Confirmed adverse events caused by RAL were definitive in the case of one mother with elevated liver enzymes (9, 10) and were suspected in two other cases with elevated liver enzymes and vomiting, respectively (11). In the infants, no adverse events and two HIV infections (1.4%) were documented. Because these data demonstrated the safety and efficacy of RAL, RAL was finally included as a preferred drug in the last updated (Aug. 6, 2015) version of the U.S. guideline (7). Moreover, our patient's plasma concentration of RAL was not significantly different in the second trimester (72 ng/mL) from that measured postpartum concentration (79.2 ng/mL), and both values were compatible with the median trough concentrations described in the U.S. guideline (72 ng/mL, range: 29-118) (8).

RAL is also known to have a high placental transfer. In the present infant, the plasma concentration of RAL was significantly higher (2,482 ng/mL) than that of the mother. Two previous case series have documented the plasma concentration of RAL in mothers and infants (12, 13). The relationship of the plasma concentration of RAL between mothers and infants is summarized in Table. In the previous reports, the concentrations of RAL in those infants were 1.63 to 15.52-fold higher than the concentrations measured in their mothers. This phenomenon agreed with our present results, although the infant/mother plasma concentration ratio of RAL in our case was the highest among the seven cases listed in Table. RAL is eliminated by glucuronidation, which is mediated by the uridine diphosphate-glucuronosyltransferase (UGT) 1A1 enzymes (8). *UGT1A1* polymorphisms vary with race, and one or two alleles of *UGT1A1*6* or two alleles of *UGT1A1*28* were found to be factors of a high concentration of RAL among Japanese patients (29). We did not study the *UGT1A1* genotype of the present mother and child because the metabolism is slow immediately after birth and increases only after several weeks of life (30). The half-life of RAL is 26.6 hours (range: 9.3-184) in infants (30). The results of a high concentration in the present infant soon after birth, and its eradication after 53 days, are compatible with those of previous reports.

In conclusion, we reported the case of a Japanese pregnant woman, who had been prescribed RAL over a long duration. Despite the detection of a high plasma concentration of RAL in her infant, no adverse events occurred. This case is the first Japanese case report to describe the plasma concentration of RAL in a mother and her infant. According to the facts of this case and a literature review, we confirmed the safety and efficacy of RAL, even in relatively early gestation. However, the efficacy of RAL for the rapid reduction of the VL was not concluded in our case because the effect of the initial regimen was not determined. The lack of data concerning Japanese mothers and infants suggests the need for further study regarding the efficacy and safety of prescribing RAL during pregnancy. In addition, the observational periods in previous studies and in our case have been short, and long-term data of children's growth are required in further research.

The Kurume University Research Ethics Committee (http://www.med.kurume-u.ac.jp/med/joint/rinri/) approved this study and written informed consent was obtained from the patient.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

The authors thank the group of pharmacokinetic studies antiretroviral drugs in Japan for measuring the concentration of drugs. We also thank all the staff members, in particular the Infection Control Nurses (Miho Miura and Fumiyo Hieda), and the staff members in the maternity ward and in the neonatal intensive care unit, for their vigorous contribution to our practice.

References

1. Research Group of Epidemic Study and Prevention for Mother-to-Child Transmission of HIV and Support for Infected Women and Children. 2013 Health, Labour and Welfare Science Research Grants Research for AIDS: Prevention Manual of Mother-to-Child Transmission of HIV. 7th ed. 2014(in Japanese).
2. Johnson M. Raltegravir use in special populations. Eur J Med Res **14**(Suppl 3): 43-46, 2009.
3. Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in

treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. Lancet **374**: 796-806, 2009.

4. Kinai E. The influence of ART drugs to the fetal growth. HIV Kansensho to AIDS no Chiryo (HIV Infection and AIDS Treatment) **4**: 41-43, 2013 (in Japanese).

5. Nakanishi M, Tanuma J, Honda M, et al. Review of 20 deliveries of HIV-positive pregnant women who didn't receive preventive measures from 1999 to 2010. Nihon AIDS Gakkaishi (The Journal of AIDS Research) **13**: 26-32, 2011 (in Japanese, Abstract in English).

6. Walmsley S, Bernstein B, King M, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. N Engl J Med **346**: 2039-2046, 2002.

7. AIDSinfo. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States (Last update August 6, 2015) [Internet]. [cited 2015 Oct 5]. Available from: https://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0

8. AIDSinfo. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents (Last update April 8, 2015) [Internet]. [cited 2015 Oct 5]. Available from: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0

9. Renet S, Closon A, Brochet MS, Bussières JF, Boucher M. Increase in transaminase levels following the use of raltegravir in a woman with a high HIV viral load at 35 weeks of pregnancy. J Obstet Gynaecol Can **35**: 68-72, 2013.

10. Boucoiran I, Tulloch K, Pick NS, et al. A case series of third-trimester raltegravir initiation: impact on maternal HIV-1 viral load and obstetrical outcomes. Can J Infect Dis Med Microbiol **26**: 145-150, 2015.

11. Watts DH, Stek A, Best BM, et al. Raltegravir pharmacokinetics during pregnancy. J Acquir Immune Defic Syndr **67**: 375-381, 2014.

12. Hegazi A, McKeown D, Doerholt K, Donaghy S, Sadiq ST, Hay P. Raltegravir in the prevention of mother-to-child transmission of HIV-1. AIDS **26**: 2421-2423, 2012.

13. McKeown DA, Rosenvinge M, Donaghy S, et al. High neonatal concentrations of raltegravir following transplacental transfer in HIV-1 positive pregnant women. AIDS **24**: 2416-2418, 2010.

14. Jaworsky D, Thompson C, Yudin MH, et al. Use of newer antiretroviral agents, darunavir and etravirine with or without raltegravir, in pregnancy: a report of two cases. Antivir Ther **15**: 677-680, 2010.

15. Pinnetti C, Baroncelli S, Villani P, et al. Rapid HIV-RNA decline following addition of raltegravir and tenofovir to ongoing highly active antiretroviral therapy in a woman presenting with high-level HIV viraemia at week 38 of pregnancy. J Antimicrob Chemother **65**: 2050-2052, 2010.

16. Taylor N, Touzeau V, Geit M, et al. Raltegravir in pregnancy: a case series presentation. Int J STD AIDS **22**: 358-360, 2011.

17. Croci L, Trezzi M, Allegri MP, et al. Pharmacokinetic and safety of raltegravir in pregnancy. Eur J Clin Pharmacol **68**: 1231-1232, 2012.

18. Westling K, Pettersson K, Kaldma A, Navér L. Rapid decline in HIV viral load when introducing raltegravir-containing antiretroviral treatment late in pregnancy. AIDS Patient Care STDS **26**: 714-717, 2012.

19. Clavel-Osorio C, Cazassus F, Stegmann S, Huc-Anaïs P, Lecam D, Peytavin G. One-month transplacental pharmacokinetics of raltegravir in a premature newborn after short-course treatment of the HIV-1-infected mother. Antimicrob Agents Chemother **57**: 6393-6394, 2013.

20. Hegazi A, Hay P. HIV seroconversion in the third trimester of pregnancy: using raltegravir to prevent mother-to-child transmission. Int J STD AIDS **24**: 245-246, 2013.

21. Cha A, Shaikh R, Williams S, Berkowitz LL. Rapid reduction in HIV viral load in late pregnancy with raltegravir: a case report. J Int Assoc Provid AIDS Care **12**: 312-314, 2013.

22. Nóbrega I, Travassos AG, Haguihara T, Amorim F, Brites C. Short communication: use of raltegravir in late-presenting HIV-infected pregnant women. AIDS Res Hum Retroviruses **29**: 1451-1454, 2013.

23. De Hoffer L, Di Biagio A, Bruzzone B, et al. Use of raltegravir in a late presenter HIV-1 woman in advanced gestational age: case report and literature review. J Chemother **25**: 181-183, 2013.

24. Adeyemo A, Wood C, Govind A. Achieving rapid reduction of HIV-1 viral load in HIV-positive pregnant women close to term - an obstetric/medical emergency: a review of three cases. Int J STD AIDS **24**: 591-592, 2013.

25. McLaughlin MM, Galal A, Ong J, Dinh M. Use of raltegravir in HIV-infected pregnant women: a case series and review of the literature. J AIDS Clin Res **5**: 386, 2014.

26. Shust GF, Jao J, Rodriguez-Caprio G, et al. Salvage regimens containing darunavir, etravirine, raltegravir, or enfuvirtide in highly treatment-experienced perinatally infected pregnant women. J Pediatric Infect Dis Soc **3**: 246-250, 2014.

27. van Halsema C, Whitfield T, Lin N, Ashton K, Torkington A, Ustianowski A. Five years' real-life experience with raltegravir in a large HIV centre. Int J STD AIDS (in press).

28. Blonk MI, Colbers AP, Hidalgo-Tenorio C, et al. Raltegravir in HIV-1-infected pregnant women: pharmacokinetics, safety, and efficacy. Clin Infect Dis **61**: 809-816, 2015.

29. Yagura H, Watanabe D, Ashida M, et al. Correlation between *UGT1A1* polymorphisms and raltegravir plasma trough concentrations in Japanese HIV-1-infected patients. J Infect Chemother **21**: 713-717, 2015.

30. Clarke DF, Acosta EP, Rizk ML, et al. Raltegravir pharmacokinetics in neonates following maternal dosing. J Acquir Immune Defic Syndr **67**: 310-315, 2014.