Use of Raltegravir in HIV-Infected Pregnant Women: A Case Series and Review of the Literature

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Abstract

Objective: To evaluate the safety and tolerability of RAL therapy and the rapidity with which RAL decreases viral load in HIV-infected pregnant women.

Methods: Women were considered for inclusion in the study if they were HIV-seropositive, ≥18 years of age, and received RAL during pregnancy. HIV viral load, CD4 count (absolute), pregnancy demographics, antiretroviral regimens, adverse events, liver function enzymes, and APGAR scores were collected.

Results: Eight HIV-infected RAL-naïve pregnant women presented between 6 to 39.4 weeks gestational age with a median RNA viral load of 41,083 copies/mL at the initiation of RAL. From the initiation of RAL until delivery, the median decline in RNA viral load was 1.60 log. At delivery, two patients reached <48 copies/mL and two had <500 copies/mL. The median RNA viral load at delivery was 911 copies/mL. No adverse events in the mother or neonate due to RAL therapy were noted during this study.

Conclusions: These results support the safe and efficacious addition of RAL to HAART regimen to decrease RNA viral load late in pregnancy if a patient is not yet virologically suppressed. Further prospective study is needed.

Keywords: Raltegravir; RAL; HIV; Pregnancy; Antiretroviral; Mother-to-child transmission; Perinatal transmission

Introduction

The rate of perinatal transmission of the human immunodeficiency virus (HIV) in the United States has decreased to 2% with the implementation of Pediatric AIDS Clinical Trial Group Protocol 076 (PACT076) treatment guidelines encouraging measures such as routine HIV counseling and testing and antiretroviral (ARV) prophylaxis [1,2]. Current Department of Health and Human Services (DHHS) guidelines recommend starting a combination of Highly Active Antiretroviral Therapy (HAART) early in pregnancy to decrease the risk of perinatal transmission. Sustaining an undetectable viral load with successful ARV regimen is of the utmost importance while also considering the safety of each ARV agent. Protease inhibitor (PI)-containing regimens, including ritonavir-boosted atazanavir or ritonavir-boosted lopinavir, are two of the recommended therapies due to existing data for safe use [1].

Raltegravir (RAL) is the first integrase strand transfer inhibitor approved by the FDA in 2007 and is classified as FDA Pregnancy Category C [3]. It is considered one of the preferred initial therapies for the treatment of HIV in adults and adolescents by the DHHS guidelines [3]. RAL demonstrates a rapid reduction of viral load [4-7] due to its antiretroviral mechanism targeting a later stage in the cell-

life cycle [8]. For this reason, RAL has also been used to reduce transmission risk during emergency surgical procedures [9].

Current DHHS guidelines recommend the use of RAL in pregnant women as an alternative agent only in special circumstances when preferred and other alternative agents cannot be used. This recommendation is based on limited pharmacokinetic and safety data in pregnancy, particularly when drug interactions with PI-containing regimens are a concern [1]. The guidelines do not recommend the use of RAL in the case of viral suppression failure presented late in pregnancy, due to the risk of developing ARV resistance [1]. In some cases, patients presenting with elevated viral loads late in pregnancy are due to non-adherence, multi-drug resistance (MDR), or new HIV diagnosis potentially making the need for a twice daily regimen unattractive to clinicians.

Practitioners are increasingly using RAL due to its unique characteristics such as overall safety and rapid decrease in viral load [10-18]. Due to an increasing number of case reports on the use of RAL in HIV-seropositive pregnant women, practitioners may choose to use RAL when other medications are not well-tolerated or unable to rapidly decrease viral load before delivery. We aim to further support the efficacy and safety of RAL in HIV seropositive (+) pregnant women and promote its use in this special population. The objective of this study is to evaluate the safety and tolerability of RAL therapy and

the rapidity with which RAL decreases viral load in pregnant women infected with HIV.

Methods

Women were considered for inclusion in the study if they were HIV-seropositive, ≥ 18 years of age, and received RAL during pregnancy. HIV viral load, CD4 count (absolute), pregnancy demographics, antiretroviral regimens, adverse events, liver function enzymes, and APGAR scores were collected. HIV viral load monitoring was performed at the infectious disease physician's discretion based on patient specific factors. The Northwestern University and Midwestern University Institutional Review Boards approved this study.

Results

Eight HIV-infected pregnant women meeting the study inclusion criteria presented between 6 and 39.4 weeks gestational age. In seven cases, RAL was added to decrease RNA viral load over a median of 6 days before delivery; in one case, RAL was used in lieu of ritonavir-boosted lopinavir due to presumed toxicity from the protease inhibitors 133 days prior to delivery. Four patients were newly diagnosed with HIV during pregnancy and were ARV naïve. All patients were RAL naïve.

In the seven cases where RAL was added to a standard HAART regimen, the regimens were emtricitabine+tenofovir+lopinivir/ritonavir+RAL (n=4), lamivudine+zidovudine+lopinivir/ritonavir+RAL (n=1), lamivudine+zidovudine+RAL (n=1) and emtricitabine+tenofovir+atazanavir/ritonavir+RAL (n=1). The other subject's regimen was emtricitabine+tenofovir+RAL. Raltegravir was added to seven patients' regimen for rapid virological suppression and to one patient due to transaminitis from lopinavir/ritonavir.

The median age of the eight subjects was 32.5 years (range 21-41). Four subjects were newly diagnosed during the pregnancy, and the other four were diagnosed 3, 6, 7, and 21 (congenitally acquired) years prior (Table 1). The patients had a median history of 3.5 gestations. The patients' median viral load at initiation of RAL was 41,083 copies/mL (range 201-351,321). Three patients had <10,000 copies/mL, four had between 10,000 and 100,000 copies/mL, and one had over 100,000 copies/mL at initiation of RAL (Table 1).

Gestational age at RAL initiation (weeks, days)	Reason for Raltegravir Use	VL at RAL initiation (copies/mL)	ARV drugs during pregnancy	Gestational age at delivery (weeks, days)	Exposure to RAL (days)	VL at delivery (copies/mL)	Decline of VL (log) from RAL initiation to delivery
38, 4	Rapid viral suppression	5, 613	FTC+TDF+ATV/r+RAL	39, 3	6	<20	2.45
38, 4	Rapid viral suppression	96, 557	FTC+TDF+LPV/r+RAL	37, 3	6	30, 84	1.50
37, 5	Rapid viral suppression	351, 321	ZVD+3TC+LPV/r+RAL	38, 6	8	7, 074	1.70
21, 1	Transaminitis from LPV/r	20,670	FTC+TDF+RAL	40, 1	133	-*	3.01
31, 1	Rapid viral suppression	61,496	ZVD+3TC+RAL	38, 1	49	911	1.83
39, 6	Rapid viral suppression	71, 660	FTC+TDF+ LPV/r+RAL	40, 1	2	13, 717	0.72
33, 3	Rapid viral suppression	201	FTC+TDF+ LPV/r+RAL	34, 1	5	66	0.48
35, 0	Rapid viral suppression	321	FTC+TDF+LPV/r+RAL	36, 2	9	26	1.09

Table 1: *Viral load not reported at delivery- viral load <20 at 21 days prior and 49 days after delivery.

The median gestational age at delivery was 38.4 weeks (range 34.1-40.1) and two of the deliveries were preterm (34 and 36 weeks). Among six subjects, the median time of exposure to RAL prior to delivery was 7 days (range 2-133) (Table 1). Two subjects were exposed at 49 and 133 days, respectively. From the initiation of RAL until delivery, there was a median decline in viral load of -1.60 log (range 0.48-3.01). Two subjects reached <48 copies/mL at delivery and two had viral loads of less than 500 copies/ml. The median viral load at delivery was 911 copies/ml (range <20-13,717, n=7). The delivery method for 5 patients was cesarean section (due to high viral load) and 3 patients underwent vaginal delivery (viral loads <20, 66, and 26 for vaginal births). The median birth weight of the neonate was 3.13 kg (range 2.21-3.70). The median APGAR score was 8 (range 7-9) and 9 for 1- and 5-minute evaluations, respectively. No significant adverse events attributed to RAL were reported of the mother or neonate that warranted discontinuation of RAL.

Discussion

Several previous case reports and case series are consistent with the current study in support of safe and efficacious use of RAL in pregnancy. These reports have shown a rapid decrease in RNA viral load during pregnancy [10-18] and good placental transfer [14,18-20]. Other studies have indicated that RAL has less protein binding [21]

and a higher penetration in the genital tract secretions than PIs [22] suggesting favorable pharmacokinetics. There is a potential for reduced neonatal clearance, possibly due to decreased neonatal uridine 5'-diphospho-glucuronosyltransferase (UGT) enzyme [14]; however, no significant adverse effects in the mother or fetus due to RAL have been reported in these studies.

RAL has been shown to be more efficacious than placebo to increase viral suppression when added to HAART therapy in the setting of MDR [23]. One patient in our study who was not virologically suppressed was suspected to have MDR, and was successfully suppressed after the addition of RAL to her therapy. RAL has also been shown to have less adverse events and better tolerability in patients than the use of PIs. One study by Cao showed RAL to be less hepatotoxic than PIs and may prevent HIV PI-induced dysregulation of lipid metabolism when added to therapy [24]. Two patients in our study had experienced elevated liver function tests and received RAL in lieu of their previous PI with improvements in liver function.

Further supporting infant safety with the use of RAL in pregnancy, teratogenicity appears to be significantly lower than that of PIs according to the Antiretroviral Pregnancy Registry published through July 2013. The number of birth defects occurring with exposure to any ritonavir-containing regimen in the 1st and 2nd or 3rd trimesters were 2.3 and 2.9%, respectively. Birth defects occurring with exposure to any RAL-containing regimen in the 1st and 2nd or 3rd trimesters were 0.02 and 0.05%, respectively [25]. This is clinically significant for the promotion of RAL use in HIV-infected pregnant women.

Limitations

Similar to prior published literature on the safety and efficacy of RAL in pregnancy, our study is limited by sample size. It is difficult to isolate the change in RNA viral load specifically attributable to RAL since our subjects were on various ARV regimens. Subjects had various lengths of exposure to RAL, ranging from 1 day to 8 months with a short median time of RAL of 7 days. Our study is also limited due to the lack of maternal and neonatal drug serum concentration data. Serum concentration data would allow better understanding of the pharmacokinetics properties of RAL. Future studies on the use of RAL in pregnancy would be improved by a larger sample of patients and obtaining drug serum concentration data. Future directions should also focus on the use of a once daily integrase inhibitor.

Conclusion

In this study, the average decrease in viral load with the addition of RAL was 1.60 log. No adverse events in the mother or neonate due to RAL therapy were noted. These results support the safe and efficacious addition of RAL to HAART regimen to decrease RNA viral load late in pregnancy if a patient is not yet virologically suppressed. These results may also suggest that RAL is a potential option when other therapies are not tolerated due to toxicities. Further prospective study with a larger population is warranted.

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