European Journal of Obstetrics & Gynecology and Reproductive Biology 157 (2011) 18–21

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Atazanavir in pregnancy: impact on neonatal hyperbilirubinemia☆,☆☆

Laurent Mandelbrot[a,b,c,*], Fabienne Mazy[d,e], Corinne Floch-Tudal[e], Françoise Meier[a], Elie Azria[b,d], Catherine Crenn-Hebert[a], Jean Marc Treluyer[f], Evelyne Herinomenzanahary[a], Claudia Ferreira[a], Gilles Peytavin[g]

[a] Assistance Publique-Hôpitaux de Paris, Louis Mourier Hospital, Department of Obstetrics and Gynecology, Colombes, France
[b] Paris 7 Diderot University, Paris, France
[c] Inserm U822, IFR69, Le Kremlin-Bicêtre F-94276, France
[d] Assistance Publique-Hôpitaux de Paris, Bichat Hospital, Department of Obstetrics and Gynecology, Paris, France
[e] Assistance Publique-Hôpitaux de Paris, Louis Mourier Hospital, Department of Neonatology, Colombes, France
[f] Assistance Publique-Hopitaux de Paris, St. Vincent de Paul Hospital, Department of Clinical Pharmacology, Paris, France
[g] Assistance Publique-Hôpitaux de Paris, Bichat Hospital, Department of Clinical Pharmacology, Paris, France

ARTICLE INFO

Article history:
Received 28 February 2010
Received in revised form 16 January 2011
Accepted 24 February 2011

Keywords:
HIV
Pregnancy
Atazanavir
Placental transfer
Neonatal hyperbilirubinemia

ABSTRACT

Objective: To study the impact on the neonate of maternal antiretroviral therapy with atazanavir (ATV).
Study design: An observational study of 22 HIV-infected women receiving, for clinical indications, antiretroviral therapy with ATV 300 mg and ritonavir 100 mg during pregnancy and their 23 HIV infants (including a twin pair).
Results: Mothers had received ATV for a median duration of 19 months [range 3–49] by delivery. At delivery, plasma HIV-RNA was <40 copies/mL in all patients. Liver enzymes were normal in 19/22 patients, but one woman had grade 3–4 liver toxicity. Maternal serum bilirubin concentrations were above the upper limit of normal in most patients, with grade 3 toxicity in 5 patients. All but one woman had trough ATV concentrations during pregnancy above the minimum effective concentration. The median cord blood ATV concentration was 130 ng/mL [range <30–758]; the cord/maternal ratio was 21%. All neonates were born at term [median 38.2 weeks]. Three neonates had mildly elevated AST transaminase levels. Bilirubin concentrations at birth were significantly higher than maternal concentrations, with a median of 44 μm/L [range 24–129]; values on days 2–3 were 63 [8–212]. Five neonates had jaundice requiring phototherapy, without liver damage, and recovered without sequelae.
Conclusion: Neonates whose mothers were treated with ATV should be monitored for hyperbilirubinemia, which may be due to placental transfer of unconjugated bilirubin from the mother and/or a direct effect of transplacental ATV on bilirubin metabolism in the fetus.

1. Introduction

Current care for pregnant women with HIV-1 infection includes use of highly active antiretroviral therapy (HAART) with boosted protease inhibitors (PI), as long-term therapy for the woman and/or for prevention of mother-to-child transmission. The benefits are well established [1,2] but there is concern about the safety of exposure to ART for the mother and for the uninfected fetus/neonate [3,4]. There are few clinical data available on the use of PIs in pregnancy, other than nelfinavir, lopinavir, saquinavir and indinavir. Thus, the other PIs are not recommended as first-line therapy for pregnant women [5,6]. Atazanavir (ATV) boosted with ritonavir is nonetheless increasingly used in pregnancy, either when women conceive on therapy, or when it is initiated in pregnancy due to resistance to first-line agents, tolerability issues or for regimen simplification. Most patients receiving boosted ATV have elevations of serum bilirubin, nearly one half with grades 3–4 levels [7], related to an increase of unconjugated bilirubin, which is due to selective inhibition of uridine diphosphate-glucuronosyl transferase (UGT1A1) [8]. This inhibition also occurs, to a lesser extent, with indinavir [9]. This has no consequence in adults, but hyperbilirubinemia could potentially be hazardous for the developing fetus and neonate. The danger of hyperbilirubinemia in neonates is well known in various conditions, such as red cell allo-immunization and congenital enzyme deficiencies [10]. High

☆ Presented in part at the 15th Conference on Retroviruses and Opportunistic Infections, Boston USA, February 3–6, 2008.
☆☆ Supported by the French National Agency for AIDS and Viral Hepatitis Research (Agence Nationale de Recherches sur le Sida et les Hépatites virales, ANRS).
* Corresponding author at: Louis Mourier Hospital, Service de Gynecologie-Obstetrique, Université Paris-Diderot, 178 rue des Renouillers, 92700 Colombes, France. Tel.: +33 147606339; fax: +33 147606338.
E-mail address: laurent.mandelbrot@lmr.aphp.fr (L. Mandelbrot).

0301-2115/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ejogrb.2011.02.005

unconjugated bilirubin concentrations can lead to damage to developing brain cells particularly in the basal ganglia and cerebellum, leading to irreversible neurological impairment, with sequelae such as ataxia, deafness or blindness.

In a study of seventeen women receiving atazanavir during the third trimester of pregnancy and postpartum, Ripamonti et al. [11] found drug concentrations of ATV similar to those reported among non-pregnant women with no dose adjustment. They also observed placental transfer of ATV, but did not study the concentrations of bilirubin. We performed a study in order to investigate the impact of *in utero* atazanavir exposure among term newborns, especially regarding hyperbilirubinemia and jaundice.

2. Materials and methods

2.1. Study design

We performed a retrospective study of HIV-1 infected women and their children who delivered in two maternities, Louis Mourier Hospital and Bichat Hospital, from July 2006 to January 2009, and who received ritonavir-boosted atazanavir during their pregnancy and delivery. All mother-infant pairs were enrolled in the ongoing French Perinatal HIV Cohort Study (EPF), with informed written consent. The cohort, sponsored by the French National AIDS Research Agency (ANRS), was approved by the Cochin Hospital Institutional Review Board and the French computer database watchdog commission (Commission Nationale de l'Informatique et des Libertés), as described elsewhere [1].

The clinicians who cared for the patients reviewed their medical records for medical history, demographics, clinical features and laboratory evaluations comprising blood cell counts, bilirubin and transaminase concentrations during pregnancy, at birth and day 3 in neonates. Women received antiretroviral therapy for clinical indications and were followed according to French national guidelines [6]. In particular, liver function tests were performed monthly during the pregnancy, including measurements of serum bilirubin, aspartate transaminase (AST) and alanine transaminase (ALT), as in all women receiving ART, as well as bilirubin, as recommended for women receiving atazanavir. Toxicities were graded according to the ACTG and US Division of AIDS table for grading severity of adult adverse experiences. Hyperbilirubinemia was defined as total serum bilirubin >17 μmol/L or unconjugated bilirubin >14 μmol/L. All women were tested for hepatitis B and C co-infection.

Neonates were monitored at birth, on day 3, and then according to the usual visits [6], and their HIV infection status was determined by polymerase chain reaction (PCR) at the age of 3 months. The measurement of bilirubin concentrations at birth was recommended for infants exposed to atazanavir. The severity of neonatal hyperbilirubinemia was defined according to values published by the American Academy of Pediatrics [12], which refer to total serum bilirubin. This grading system was designed to predict the risk of kernicterus in neonates with hemolytic anemia. Therapeutic drug monitoring of atazanavir serum concentrations was performed by some clinicians in the third trimester of pregnancy as part of clinical care, and also at the time of delivery.

Placental transfer was determined by calculating the fetal/maternal ratio of drug concentrations in blood samples simultaneously collected from the umbilical vein and a peripheral maternal vein at delivery. Serum concentrations of atazanavir were measured using HPLC coupled with PDA-UV detection (LOQ 30 ng/mL), with a C_{min} therapeutic range considered to be between 200 and 800 ng/mL [6]. ATV concentrations in maternal and cord blood serum were compared using Student's *t*-test for paired series and correlation test.

3. Results

3.1. Maternal characteristics (Table 1)

Twenty-two HIV-1 positive pregnant women and 23 infants (including a dichorionic diamniotic female twin pair) were included in the study. The median maternal age was 33 years [range 25–41], the median time since HIV-1 diagnosis was 6.8 years [range 7 months to 17 years]. All of the women received combination antiretroviral therapy for clinical indications with boosted ATV, for a median duration of 21.6 months [range 3–49] through to delivery. ATV was started before the pregnancy in 18/22 patients, and none interrupted the therapy during pregnancy, delivery or the post-partum period. One patient had hepatitis B infection, and none of the women had hepatitis C infection, a history of ethanol abuse or other pre-existing liver disease. In addition to atazanavir 300 mg with ritonavir 100 mg once daily, one woman received nevirapine, two received another PI, and all women received two nucleoside or nucleotide reverse transcriptase inhibitors: ten zidovudine–lamivudine, six tenofovir with or without emtricitabine, and the others various combinations of didanosine, abacavir, zidovudine, lamivudine, emtricitabine. All women received intravenous zidovudine (2 mg/kg loading dose, followed by 1 mg/kg/h) during labor and delivery and all neonates received 4–6 weeks of zidovudine prophylaxis, according to standard recommendations [6].

Maternal HIV RNA load was undetectable (<40 copies/mL) in all of the women by the time of delivery. The median $CD4^+$ cell count was 491 [range 221–971] cells/μL at delivery.

Maternal serum bilirubin concentrations were above the upper limit of normal during pregnancy and/or delivery in 17/21 patients (data missing for 1 patient), grade 1–2 in 12 patients and grade 3 toxicity in 5 patients.

Alanine aminotransferase (ALT) levels were normal during pregnancy and delivery in 19/22 patients, showed grade 1 elevations (55 and 66 IU/mL, respectively) in 2 women and grade 3 toxicity in one woman. This patient had liver enzymes 10 times the normal value in the third trimester of pregnancy (AST 303, ALT 456 IU/mL); work-up was negative for viral hepatitis, gallbladder disease, pre-eclampsia intrahepatic cholestasis of pregnancy and other causes of cytolysis. The patient was receiving a 5-drug regimen including nevirapine, but the liver enzymes did not

Table 1
Maternal biological results during pregnancy and delivery (median, range), $n = 22$.

	Second trimester	Third trimester	At delivery
CD4 (cells/μL)	366 [103–959]	500 [186–971]	491 [221–971]
Undetectable viral load <40 copies/mL at delivery (%)	79	86	100
Total serum bilirubin (μmol/L)	30 [7–106]	26 [3–89]	33 [8–96]
Unconjugated bilirubin (μmol/L)	29 [16–80]	28 [15–78]	30 [15–89]
Aspartate aminotransferase (IU/L)	21 [12–151]	23 [11–236]	25 [17–303]
Alanine aminotransferase (IU/L)	14 [5–248]	12 [7–456]	16 [7–467]