Patricia Izurieta
Tibotec BVBA
Mechelen
Belgium
pizuriet@ITS.JNJ.com

Safety and pharmacokinetics of etravirine in pregnant HIV-infected women

Patricia Izurieta,[1] Thomas N Kakuda,[2] Andrew Clark,[3] Caroline Feys,[1] James Witek[2]

[1]Tibotec BVBA, Mechelen, Belgium; [2]Tibotec Inc., Yardley, PA, USA; [3]Johnson & Johnson, High Wycombe, UK

PE4.1/6

Abstract

Objectives

Etravirine (ETR; TMC125) is a next-generation NNRTI with demonstrated activity in treatment-experienced, HIV-1-infected adults. As pregnancy data with ETR is limited, an assessment of available pharmacokinetic (PK) and safety data in pregnant women was undertaken.

Methods

ETR was available via compassionate use to pregnant women in need; PK assessments during the third trimester were requested. Blood samples were collected predose, 1, 3, 6 and 12 hours post-dose. Plasma ETR concentrations were determined using a validated high performance liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) assay. PK parameters were obtained by non-compartmental analysis and compared to historical control. Women were followed until delivery and whenever possible, cord blood samples were obtained.

Results

Five women participated in the PK evaluation. Three women were exposed to ETR throughout their pregnancy and two during the third trimester only. Individual PK parameters are as follows:

	t_{max} (h)	C_{max} (ng/mL)	AUC_{12h} (ng•h/mL)	C_{0h} (ng/mL)
Case 1	3	896	4,277*	387
Case 2	6	1,210	6,448*	521
Case 3	3	474	4,788	149
Case 4	3	1,150	8,870	898
Case 5	3	445	3,041	434
Mean	–	835	5,485	478
SD	–	363	2,253	272
Historical control (DUET population PK, n=575)				
Mean	–	–	5,506	393
SD	–	–	4,710	391

*AUC_{6h}; t_{max} = time-to-reach the maximum plasma concentration; c_{max} = maximum plasma concentration; AUC_{12h} = area under the plasma concentration-time curve from time of administration to 12 hours after dosing; C_{0h} = predose plasma concentration; SD = standard deviation

Among the five pregnancies, three Caesarean sections were performed, one pre-term due to twin pregnancy, the remaining two were normal deliveries. All babies were healthy, one baby was born with an accessory auricle, but otherwise normal. There were no other malformations or other abnormal findings. Post-partum ETR cord blood concentration in Case 5 was 112ng/mL, whereas the corresponding plasma concentration was 339ng/mL. Three mothers had undetectable HIV-RNA at delivery; no data was available for the remaining two mothers. Two babies were HIV-DNA negative (two twins) and one baby had undetectable HIV-RNA at delivery, no data is available for the remaining three babies.

Conclusions

ETR pharmacokinetics in five pregnant women were comparable to those of non-pregnant adults suggesting no ETR dose adjustment is needed during the third trimester. Although data on exposure to ETR during pregnancy is limited, this data suggests that ETR may not have an effect on foetal or neonatal toxicity. Further evaluation of ETR pharmacokinetics in pregnant women is ongoing (TMC114-HIV3015: clinicaltrials.gov NCT00855335).

Introduction

- The next-generation NNRTI ETR is predominantly metabolised by the cytochrome P450 (CYP) enzymes CYP3A, CYP2C9 and CYP2C19, followed by glucuronidation; it is an inducer of CYP3A4 and an inhibitor of CYP2C9, CYP2C19 and P-glycoprotein[1]
- Two Phase III trials (DUET-1 and DUET-2) demonstrated significant antiviral benefit over 96 weeks of treatment with ETR in treatment-experienced patients with resistance to first-generation NNRTIs[2]
  - except for a higher incidence of rash, patients treated with ETR had a safety and tolerability profile similar to placebo[3]

Background

- The potential for ETR to affect the reproductive system was studied in rats and rabbits
  - ETR dosed up to 500mg/kg/day did not affect fertility and early embryonic development in rats
  - no teratogenicity was observed in rats (up to 1,000mg/kg/day) or rabbits (up to 375mg/kg/day)
  - systemic exposures in the reproductive toxicology studies were equivalent to human exposure
- As pregnancy data with ETR are limited, an assessment of ETR pharmacokinetics and outcome data available in pregnant women was undertaken
  - ETR was available via compassionate use to pregnant women in need during the clinical development programme

PK analyses

- PK assessments were carried out during the third trimester and/or at time of birth in pregnant women receiving ETR in combination with other ARVs
- Blood samples were collected pre-dose and 1, 3, 6 and 12 hours post-dose
- Plasma concentrations of ETR were determined using a validated LC-MS/MS method (LLOQ 2ng/mL)
- A non-compartmental model with extravascular input was used for the PK analysis
- PK analysis was performed using WinNonlin Professional™ (version 5.1, Pharsight Corporation, Mountain View, California, USA)
- Comparison was made with population PK data from DUET-1 and DUET-2[4]
  - PK parameters between men and women were not significantly different

ARV = antiretroviral; LLOQ = lower limit of quantification

Patient characteristics

Case number	Age	Trimester of exposure to ETR	Concomitant ARV medication
1	32	First trimester until delivery	DRV/r + 3TC
2	38	Third trimester until delivery	DRV/r + TVD + ENF
3	19	First trimester until delivery	DRV/r + TDF + ENF
4	41	Third trimester until delivery	DRV/r + TRV
5	42	First trimester until delivery	DRV/r + TDF + ZDV + 3TC

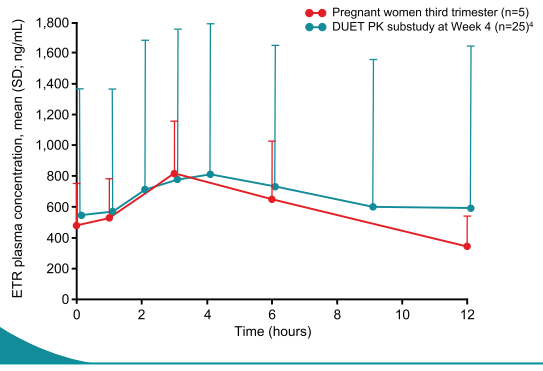
DRV/r = darunavir with low-dose ritonavir; 3TC = lamivudine
TVD = Truvada®; ENF = enfuvirtide; TDF = tenofovir disoproxil fumarate; TRV = Trizivir®; ZDV = zidovudine

Patient outcome

Case number	Pregnancy outcome	Babies' outcome and other data
1	Healthy baby via normal delivery	Mother had undetectable viral load at delivery; baby received ZDV for prophylaxis
2	Premature healthy twins via Caesarean section	Mother and babies had undetectable viral load at delivery; babies' PCR negative at 4 months
3	Healthy baby via Caesarean section	At 14 days, baby had undetectable viral load; mother had undetectable viral load at delivery
4	Healthy baby via Caesarean section	Baby received ZDV for prophylaxis; mother's data not reported
5	Healthy baby via normal delivery	Baby received ZDV + 3TC for prophylaxis; mother's data not reported; post-partum ETR cord blood concentration was 112ng/mL, whereas the corresponding maternal blood plasma concentration was 339ng/mL

PCR = polymerase chain reaction

ETR plasma concentration-time profile in pregnant women



PK parameters of ETR in third trimester

Case number	t_{max} (hours)	C_{max} (ng/mL)	AUC_{12h} (ng•h/mL)	C_{0h} (ng/mL)
1	3	896	4,277*	387
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*Values are AUC_{6h}

Safety summary

- Among the five pregnancies
  - three Caesarean sections were performed (one pre-term due to twin pregnancy)
  - two babies were born by vaginal delivery
- All babies were healthy; one baby was born with polyotia (a small accessory auricle on the right ear) but was otherwise normal on physical examination
  - no other malformations or other abnormal findings were detected

Conclusions

- ETR PK parameters in five pregnant women were comparable with those of non-pregnant adults, suggesting no ETR dose adjustment is needed during the third trimester
- Although clinical data on exposure to ETR during pregnancy is limited, ETR did not have an effect on foetal or neonatal toxicity in this case series
- Further evaluation of ETR PK in pregnant women is ongoing (trial NCT00855335)
  - this study will investigate the PK parameters of ETR and/or DRV/r during the second and third trimesters of pregnancy and up to 12 weeks post-partum
  - changes in ARV activity, safety and tolerability during pregnancy and post-partum will be examined

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Acknowledgements and disclosures

- The authors would like to express their gratitude to the patients. They also acknowledge
  - V Hillewaert, J&J Pharmaceutical Research and Development, Beerse, Belgium
- Editorial support was provided by Emily de Looze of Gardiner-Caldwell Communications, Macclesfield, UK; this support was funded by Tibotec
- PI, TNK, CF and JW are full-time employees of Tibotec. AC is a full-time employee of Johnson & Johnson

Presented at the 12th European AIDS Conference, Cologne, Germany, 11–14 November 2009.

This poster is available on-line at www.tibotec.com