Establishing a Treatment Dose of Nevirapine for Full-term Neonates with Perinatal HIV Infection: IMPAACT P1115

LBPE011

Chadwick EG[1], Qin M[2], Bryson Y[3], Mirochnick M[4], Ruel T[5], Zadzilka A[6], Coletti A[7], Zimmer B[6], Tierney C[2], Persaud D[8], Cotton MF[9], Jean-Philippe P[10], Hazra R[11], Jennings C[12] and Capparelli EV[13] for the IMPAACT P1115 Team

[1]Northwestern University's Feinberg School of Medicine, Chicago, Illinois, USA; [2,2]Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA; [3]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [4]Boston Medical Center, Boston, MA, USA; [5]University of California, San Francisco, San Francisco, CA, USA; [6,6] Frontier Science and Technology Research Foundation, Amherst, NY, USA; [7]360, Durham, NC, USA; [8]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [9] FAMCRU, Stellenbosch University, Tygerberg, South Africa; [10]Henry Jackson Foundation, National Institute of Allergy and Infectious Diseases/Division of AIDS, NIH, Bethesda MD, USA; [11]Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, Bethesda, MD, USA; [12]Rush University Medical Center, Chicago, IL, USA; [13]University of California, San Diego, San Diego, CA, USA

Abstract

Background: Very early treatment of HIV-infected neonates may sufficiently limit HIV reservoirs to enable HIV remission after cessation of combination antiretroviral therapy (cART). However, there are limited data on therapeutic concentrations of antiretroviral drugs approved for neonatal use.
Methods: IMPAACT P1115 is an ongoing multinational trial investigating very early cART and HIV remission in infected neonates. Pharmacokinetic (PK) modeling from prior neonatal nevirapine (NVP) prophylaxis data suggested that NVP dosing of 6 mg/kg/dose twice daily (BID) would maintain concentrations between 3-10 mcg/mL, the established therapeutic range.
Zidovudine+lamivudine+NVP were initiated at <48 hours of age in neonates of HIV-infected mothers untreated during pregnancy, before determination of infant infection status. Single PK samples from 1 +/- 2 weeks on study were assayed for NVP concentrations using high performance liquid chromatography. Plasma NVP exposures and safety were examined among enrolled neonates ≥37 weeks gestational age.
Results: 30 neonates (median gestation 38 weeks) were studied; 20 boys/10 girls from Africa (n=24), South America(3), North America(2) and Asia(1). cART started on the day of birth in 19, and 2/30 were HIV-infected. Five participants had toxicities ≥Grade (Gr) 2 at least possibly related to cART: 1 w/Gr 2 ANC; 1 w/Gr 2 and 1 w/Gr 4 hemoglobin; 2 w/Gr 2 ANC + Gr 2 hemoglobin. No rashes or elevated transaminases occurred. Mean (SD) plasma NVP concentration was 9.2 (5.6) mcg/mL at Week 1 (n=28) and 4.3 (3.3) at Week 2 (n=7). (Figure) Overall, 83% of samples were >3.0 mcg/ml; while 43% of Week 1 NVP levels were >10mcg/mL, most were ≤15 mcg/mL.
Conclusions: Therapeutic NVP dosing of 6 mg/kg/dose BID in full-term newborns appears to be safe and maintains NVP concentrations >3 mcg/ml over the first 2 weeks of life in the majority of infants. These data support the continued study of this NVP dosing regimen to treat neonates.

Background

- Very early combination antiretroviral treatment (cART) in HIV-infected neonates may limit seeding of viral reservoirs to enable HIV remission after cessation of cART.
- Nevirapine (NVP) is one of few highly active ARVs available in liquid formulation which can be utilized for very early treatment of infants
- NVP safety and dosing in neonates is well established for prophylaxis: target is 0.1mcg/mL (based on IC50)
- Prophylaxis dosing does not achieve established therapeutic range NVP concentrations (3-10 mcg/mL)
- NVP troughs <3 mcg/mL have been associated with clinical failures (deVries Sluijs et al Clin PK 2003)
- Pharmacokinetic (PK) modeling from existing neonatal and older infant NVP PK data suggest that NVP at 6 mg/kg/dose twice daily would maintain concentrations in the established therapeutic range
  - This dose was selected for study in P1115, with target plasma concentrations of 3-10 mcg/mL

Study Design

- IMPAACT P1115 is an ongoing Phase I/II proof of concept study to explore very early intensive treatment of HIV-infected neonates to achieve HIV remission
- Population: Neonates of mothers with HIV infection untreated during pregnancy, enrolled in P1115 before determination of infant infection status
- Treatment: Zidovudine, lamivudine and NVP initiated within 48 hours of age
  – NVP dose: 6 mg/kg/dose twice daily until HIV status determined; if not HIV-infected, NVP was reduced to prophylaxis dosing
- PK: Single plasma samples from Week 1 and, if still taking NVP at study doses, Week 2 were assayed for NVP concentrations using high performance liquid chromatography
- Plasma NVP exposures and safety over the first 2 weeks of life were examined among enrolled neonates ≥37 weeks gestational age

Baseline Demographics

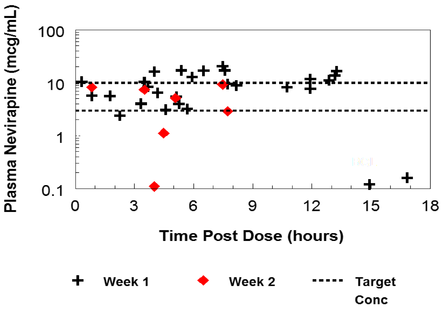
Neonates	N=30
Median (range) Gestational age	38 (37-40) weeks
Median (range) birth weight	3.1 (2.8-3.3) kg
Sex, n (%) Boys Girls	 20 (33.3%) 10 (67.7%)
Geographic region Africa N. America S. America Asia	 24 (80%) 3 (10%) 2 (6.7%) 1 (3.3%)
Age at cART initiation Day 0 Day 1	 19 (63.3%) 11 (36.7%)
In utero HIV infection No Yes	 28 (96.7%) 2 (6.7%)

Plasma NVP Concentrations (mcg/mL)

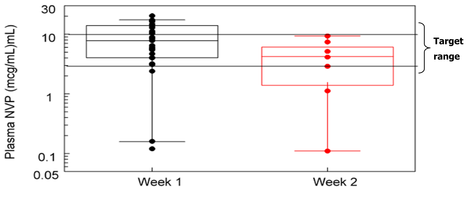
	N	Mean (SD)	Median	Min	Max	% Within Target	% Above Target	% Below Target
Week 1*	28	9.2 (5.6)	8.7	0.12	20.4	46%	43%	11%
Week 2^	7	4.3 (3.3)	4.1	0.1	9.3	57%	-	43%

* 2 neonates did not have Week 1 samples
^ Only 7 neonates were still taking 6mg/kg/dose of NVP by Week 2

Plasma NVP Concentrations at Time Post



NVP Concentrations By Week



Neonates with ≥ Grade 2 Toxicities Through Week 2 at Least Possibly Related to Treatment Regimen*

N (%)	Hemoglobin (Hgb)	Absolute Neutrophil Count (ANC)
2 (6.7%)	Grade 2	Grade 2
1 (3.3%)	Grade 2	-
1 (3.3%)	Grade 4	-
1 (3.3%)	-	Grade 2
Total = 5/30 (16.7%) had at least one toxicity	3 Grade 2, 1 Grade 4 Hgb	3 Grade 2 ANC

*All hematologic toxicities were judged to be related to ZDV
•No ≥ Grade 2 treatment-related rashes or elevated transaminases

Summary

- NVP dosed at 6mg/kg BID achieved minimum therapeutic concentrations of ≥3 mcg/mL within the first week of life in 25/28 (89%) neonates ≥37 weeks gestation
- NVP concentrations exceeded the upper limit of the target range in 43% of infants at Week 1
  - However, among the 7 neonates sampled at Week 2, none exceeded the target range and 57% achieved target
- This NVP dose was well-tolerated and appears to be safe in this age group

Discussion

- A lower NVP dose of 4mg/kg BID might better maintain peak levels in the target range through the first week of life, but PK modeling (data not shown) suggests it would lead to a higher frequency (>33%) of sub-therapeutic levels, which carries risk of virologic rebound and NVP resistance. In addition, NVP concentrations are known to fall rapidly in the first weeks of life due to maturation of metabolism and auto-induction, underscoring the challenge of NVP dosing in neonates.
- The strategy of dosing at NVP 6 mg/kg/dose BID appears to be safe and minimizes sub-therapeutic NVP exposure; these data support the continued study of this NVP dosing regimen to treat neonates.

References

. de Vries-Sluijs TE, Dieleman JP, Arts D, et. al. Clin PK. 42(6):599-605, 2003.
. Mirochnick M, Capparelli E, Nielsen K, et. al. Nevirapine pharmacokinetics during the first year of life: A population analysis across studies. Ped Acad Soc Mtg, San Francisco, CA, May, 2006.
. Mirochnick M, Nielsen-Saines K, Pilotto JH et. al. Nevirapine Dosing for Treatment in the First Month of Life. 23rd CROI, Boston, MA, Feb 2016

Funding

• Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Acknowledgments

The IMPAACT P1115 study team wishes to thank all the patients, families and investigators participating in this trial