Safety and Pharmacokinetics of a Potent Anti-HIV Monoclonal Antibody, VRC01, in HIV-Exposed Newborns

Coleen K. Cunningham[1], Elizabeth J. McFarland[2], Edmund V Capparelli[3], Petronella Muresan[4], Charlotte Perlowski[5], Megan Valentine[5], Betsy Smith[6], John R. Mascola[7], and Barney Graham[7], for the IMPAACT P1112 team

1. Dept. of Pediatrics, Duke University Medical Center, Durham, NC; 2. Dept. of Pediatrics, University of Colorado School of Medicine, Aurora, CO; 3. UCSD Pediatrics; 4. Center for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, Boston, MA; 5. FHI360, Durham, NC; 6. Division of AIDS, NIAID, NIH, Rockville, MD; 7. Vaccine Research Center, NIAID, NIH, Rockville, MD

Abstract

Background- Despite advances in the use of antiretroviral therapy (ART) to prevent mother to child HIV transmission (MTCT), children still become infected for a variety of reasons. A long acting monoclonal antibody might provide a strategy to further prevent transmission.

Methods- This is an ongoing, prospective, open label, dose escalating study of a HIV neutralizing, monoclonal antibody, VRC01, administered as a single 20 or 40 mg/kg subcutaneous (SC) dose within 72 hours of birth to infants at increased risk of HIV transmission. Healthy infants and their mothers receive ART as indicated to prevent MTCT. Infants complete safety assessments over 4 hours immediately after dosing and then have safety and pharmacokinetic (PK) measures at 24 hours, days 3, 7, 14, 28, weeks 8, 16 and 24. A non-compartmental PK analysis is used except for CL./F and Vss/F which are estimated using a 2-compartment model. Target VRC01 level is 50 mcg/mL on day 28.

Results- Both dose groups are fully accrued (13 each) from 10 sites in the continental US, Puerto Rico, and South Africa. Approximately half enrollees are male (56%) and black (52%). VRC01 was administered soon after birth, at a mean age of 1.8 (SD 1.0) days. Most infants (12/13) in the lower dose group received a single injection (average volume 0.6 mL) while 12/13 infants in the higher dose group received two injections (average volume 0.7 mL). Safety data are available for 25/26 subjects and PK data through day 28 for the lower dose are available for 12/13 (one child was under-dosed and excluded from PK analysis). Overall, VRC01 was well tolerated with no attributable serious systemic reactions. Local reactions were common, occurring in six (46%) and nine (75%) infants in the low and high dose groups, respectively. None of the local reactions were serious and 100% and 90% in the 20 and 40 mg dose groups, respectively, resolved within four hours of injection. Pain at the injection site was reported in only two infants, both grade 1. The PK measures for 12 infants in the 20 mg/kg group are as follows.

Pharmacokinetic measure	MEAN	STD DEV	MEDIAN	MIN	MAX
Day 28 VRC01 level (mcg/mL)	40.2	15.2.	39.2	16.7	75.6
Maximum concentration (mcg/mL)	234.7	43.5	233.3	153.6	333.0
CL/F (L/d/kg; apparent clearance)	0.0049	0.0013	0.0049	0.0033	0.0067
Vss/F (L/kg; apparent volume of distribution)	0.16	0.01	0.15	0.14	0.16
Serum half-life (d)	19.0	5.1	19.6	10.4	28.6
Time at maximum concentration (d)	2.4	1.89	1.6	0.9	6.11

Conclusion- These preliminary results indicate that VRC01 administered to neonates via the SC route is safe and well tolerated. The PK for the lower dose demonstrate circulating antibody through day 28 of life close to but below the target in 9/12 (75%). The half-life of VRC01 would support monthly injections for infants at ongoing risk of HIV infection through breastfeeding.

Methods

This is an ongoing, prospective, open label, dose escalating study of a monoclonal antibody, VRC01, administered as a single 20 or 40 mg/kg subcutaneous (SC) dose within 72 hours of birth to infants born to HIV-1-infected women who were:

- ≥ 36 weeks gestation;
- ≥ 2kg birth weight; and
- met the study definition of increased risk of HIV infection.

Increased risk of HIV acquisition was defined as documentation of one or more of the following risk factors in the mother:

- Received no ARV during pregnancy; or
- Began or reinitiated ARV (after interruption of >14 days), during the third trimester; or
- Any detectable viral replication at last measurement prior to delivery (within 30 days of delivery); or
- Prolonged rupture of membranes (> 12 hours); or
- Documented 2-ARV class resistant HIV infection

Only the infants received the VRC01 immunization. Infants completed safety assessments for 4 hours after dosing and then had safety and/or PK measures at 24 hours, days 3, 7, 14, 28, weeks 8, 16 and 24.

All infants received prophylactic ARV treatment per local standard of care.

Results

ENROLLMENT

27 children were enrolled from ten sites; one child in 20 mg/kg Dose Group was incorrectly enrolled: Absolute neutrophil count of 3150 at birth was less than the required 4000 for eligibility. One child in 40 mg/kg Dose Group was under-dosed at 40 mg instead of 70 mg. This child was excluded from the PK analysis.

Institution	Dose 20mg/kg # enrolled	Dose 40mg/kg # enrolled
Bronx-Lebanon Hospital	2	0
University of CA, Los Angeles	1	1
Emory University	0	2
Cape Town Family Clinical Research Unit	1	5
Jacobi Med. Ctr.	2	2
Johns Hopkins University	1	1
San Juan, Puerto Rico	1	0
South Florida, Ft Lauderdale	2	2
University of Colorado	2	1
University of Puerto Rico	1	0
Total	**13**	**14**

BASELINE CHARACTERISTICS

Characteristic		20mg/kg (N=13)	40mg/kg (N=14)	Total (N=27)
Gender	Male	8 (62%)	6 (43%)	14 (52%)
Race	Black	6 (46%)	11 (73%)	17 (61%)
	White	6 (46%)	2 (13%)	8 (29%)
	Unknown	1 (8%)	2 (13%)	3 (11%)
Ethnicity	Hispanic/Latino	3 (23%)	4 (27%)	7 (25%)
	>1 or unknown	2 (15%)	1 (7%)	3 (11%)
Infant ARV Regimen	3TC,ZDV	1 (8%)	0 (0%)	1 (4%)
	3TC,ZDV,NFV	1 (8%)	0 (0%)	1 (4%)
	3TC,ZDV,NVP	2 (15%)	5 (36%)	7 (26%)
	NVP	0 (0%)	1 (7%)	1 (4%)
	ZDV	4 (31%)	4 (29%)	8 (30%)
	ZDV,NVP	5 (38%)	4 (29%)	9 (33%)
Age (days)	Mean (SD)	1.5 (1.1))	1.9 (0.9)	1.7 (1.0)
	Median	2	2	2
	Min, max	0, 3	0, 3	0, 3
Weight at birth (grams)	Mean (SD)	3185 (703)	3100 (242)	3143 (517)
	Median	3045	3160	3105
	Min, max	2330, 4675	2609, 3390	2330, 4675

Safety and PK

SAFETY: VCR01 was well tolerated.

WITHIN 30 DAYS OF IMMUNIZATION

Six (22%) participants experienced a total of eight Grade 3+ adverse events (AEs); none were treatment-related:

- Four had a Grade 4 AEs:
  - In the 20mg/kg group, two (14%) had abnormal neutrophil count.
  - In the 40 mg/kg group, one had abnormal potassium and one had abnormal total bilirubin.
- Two had grade 3 AEs including increased bilirubin, abdominal symptoms, and bronchiolitis.
- The events were distributed evenly between groups.

GREATER THAN 30 DAYS PAST IMMUNIZATION

There were no Grade 4 AEs.

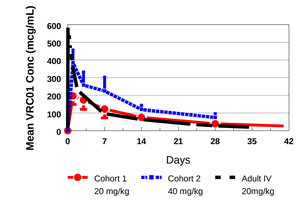
Three (11%) participants in the 20 mg/kg Dose Group had Grade 3 AEs including pneumonia and bronchiolitis (1), fever (1), and bronchiolitis (1); none were treatment-related.

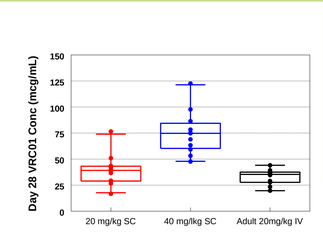
LOCAL REACTIONS

Statistic	Local reaction	Dose 20mg/kg N (%) N (Min/Max)	Dose 40mg/kg N (%) N (Min/Max)
Total # children	N	13	14
Total # injection sites	N	14	26
Volume/inject site (mL)	Mean	0.6	0.7
# children with specified reaction	Any local reaction	6	11
	Edema	2	4
	erythema/redness	5	8
	induration	2	7
	bruising	1	3
Grade average (min/max)	Any local reaction	1.2 (1/2)	1.4 (1/2)
	edema	1.0 (1/1)	1.0 (1/1)
	erythema/redness	1.0 (1/1)	1.4 (1/2)
	induration	1.5 (1/2)	1.6 (1/2)
	bruising	1.0 (1/1)	1.0 (1/1)
Size average in cm (min/max)	edema	1.5 (0.9/2.0)	1.4 (0.5/2.0)
	erythema/redness	0.7 (0.5/1.0)	2.2 (1.0/3.3)
	induration	1.6 (0.5/2.7)	2.5 (0.2/5.0)
% resolved by 4 hours	Any local reaction	6 (100.0%)	6 (54.5%)
	edema	2 (100.0%)	4 (100.0%)
	erythema/redness	5 (100.0%)	7 (87.5%)
	induration	2 (100.0%)	3 (42.9%)
	bruising	0 (0.0%)	0 (0.0%)
Average duration of reaction (hours)	Any local reaction	2.0	16.4
	edema	1.0	0.6
	erythema/redness	2.1	4.3
	induration	2.5	21.7
	bruising	72.0	128.0

PHARMACOKINETICS

Figures demonstrates levels after single 20 or 40 mg/kg SC dose compared to adults receiving 20 mg/kg IV.





VRC01	DOSE	MEAN	SD	MEDIAN	MIN	MAX
C28D (mcg/mL)	20 mg/kg	39.33	14.94	39.19	16.71	76.56
	40 mg/kg	75.22	21.38	74.79	47.61	122.59
C_{max} (mcg/mL)	20 mg/kg	226.64	30.78	233.32	153.63	260.64
	40 mg/kg	378.37	79.20	390.27	247.44	536.60
T_{max} (d)	20 mg/kg	2.7	2.2	2	1	7
	40 mg/kg	1.4	0.8	1	1	3
Half-life (d)	20 mg/kg	19.73	4.99	20.17	13.11	28.60

Conclusion

These preliminary results demonstrate that VRC01 administered as a single dose to neonates via the SC route is safe and well tolerated. The PK measures demonstrate persistent levels of drug through day 28 of life, with the 40 mg/kg dose achieving the target level at day 28. The half-life of VRC01 supports monthly injections for infants at ongoing risk of HIV infection through breastfeeding.

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