Life on the Front Lines of Ebola: *Transfusion Medicine Lessons Learned and Creation of a National Inventory of Ebola Convalescent Plasma*

Annie Winkler MD, MSc
Assistant Professor, Emory University Department of Pathology and Laboratory Medicine
Medical Director, Grady Health System Transfusion Service
Assistant Medical Director, Emory Special Coagulation Laboratory

American Society for Apheresis Meeting
San Antonio, Texas
May 9, 2015
Disclosures

• Cerus Corporation
  – Honoraria
  – Laboratory Equipment

• Fresenius Kabi
  – Laboratory Equipment
Treatment of Ebola Virus Disease

• Without a licensed vaccine or other treatment, Ebola virus disease (EVD) management has been limited to supportive care and barrier methods to prevent transmission
  – Supportive care including fluid and electrolyte replacement, and management of secondary symptoms

• Despite these interventions, the 2014 West Africa epidemic has become the deadliest occurrence of the disease, killing five times more than all other known Ebola outbreaks combined

• While devastating, this epidemic has allowed for the opportunity to investigate experimental agents in clinical trials
# Experimental Interventions

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism</th>
<th>Status</th>
</tr>
</thead>
</table>
| **Convalescent Plasma**        | Provide passive immunization with anti-EBOV antibodies                     | • Purified polyclonal IgG has been shown to be protective in nonhuman primate model  
• No proven efficacy in humans  
• Has been used in multiple evacuated patients during West Africa 2014 outbreak |
| **Hyperimmune Globulin**       | Concentrated IgG to provide high titers of neutralizing antibody           | • Not currently available.                                            
• Work in horses and cattle are underway  
• Ongoing efforts in West Africa (Grifols®) |
| **ZMapp (Mapp Biopharmaceutical)** | Cocktail of three chimeric mouse human monoclonal antibodies (c13C6+c2G4+c4G4) targeting the GP envelope protein | • Very promising data in nonhuman primates  
• No human trials  
• In limited supply |
| **TKM-Ebola (TKM-100802; Tekmira)** | Nanoparticle Small interfering Ribonucleic acid (siRNA)  
Targets two essential viral genes to stop the virus from replicating | • Very promising data in nonhuman primates  
• Single-dose phase 1 study in healthy volunteers found side effects including headache, dizziness, chest tightness and raised heart rate at high doses; on partial hold by FDA  
• In limited supply |

Dye JM. *Proc Natl Acad Sci U S A* 2012; 109, 5034-5039  
Qui X. *Nature* 2014; 514, 47-54  
Thi EP. *Nature* 2015; epub ahead of print
## Experimental Interventions

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism</th>
<th>Status</th>
</tr>
</thead>
</table>
| AVI 7537 (Sarepta)        | Phosphorodiamidate oligonucleotide                                         | • Monkey studies showed 60-80% survival when given at the time of infection  
• Tolerability has been demonstrated in early studies.  
• No human grade available |
| Favipiravir (T-705; Toyama Chemical) | Selective inhibition of viral RNA-dependent RNA polymerase  
Does not inhibit RNA or DNA synthesis in mammalian cells | • Effective against EVD in mice, but in monkey study only 1/6 survived  
• Approved in Japan for influenza treatment under special circumstances  
• In clinical trials in Guinea |
| BCX4430 (Biocryst Pharmaceuticals) | Viral RNA-dependent RNA polymerase inhibitor                               | • 83-100% survival in rodents with EVD  
• Testing for EVD in monkeys is underway |
| Brincidofovir (CMX001, Chimerix) | Lipid conjugate of the nucleotide analog, cidofovir                     | • In vitro data at CDC showing good anti-EBOV activity  
• Has been used in multiple evacuated patients during West Africa 2014 outbreak  
• As of 1/205 manufacturer has withdrawn support for West Africa trials and ended discussion of future trials |
Treatment of Ebola Virus Disease

• One of the first experimental agents used to treat EVD patients in the US and Europe was ZMapp™, a drug cocktail comprised of individual monoclonal antibodies targeted against the Ebola Virus.

• A limited supply of ZMapp™ was used to treat 7 individuals infected with EVD.

• However, in August 2014 the limited supply of ZMapp™ had been exhausted.
# Possible Predictors of Clinical Outcomes in EVD

<table>
<thead>
<tr>
<th>Nonlethal Infection</th>
<th>Lethal Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prominent CD8(^+) T cell activation</td>
<td>No CD8(^+) T cell activation</td>
</tr>
<tr>
<td>Above-normal numbers of T cells</td>
<td>Below-normal numbers of T cells</td>
</tr>
<tr>
<td>(10^7) viral genome copies/ml serum</td>
<td>(10^{10}) viral genome copies/ml serum</td>
</tr>
<tr>
<td><strong>Detectable antibodies in blood at onset of symptoms</strong></td>
<td>No detectable antibodies in blood at onset of symptoms</td>
</tr>
<tr>
<td>Low Nitric Oxide</td>
<td>High Nitric Oxide levels</td>
</tr>
<tr>
<td>High sCD40L levels</td>
<td>Low sCD40L levels</td>
</tr>
</tbody>
</table>

Sanchez A. *J Virol* 2004; 78, 10370-10377  
Rollin PE. *J Infect Dis* 2007; 196, S364-371  
McElroy AK. *J Infect Dis* 2014; 210, 558-566
Longitudinal Trends in EBOV PCR, Antibodies and Symptoms

- Natural serologic response to EVD has been well characterized.
- IgM responses are detected as early as 2 days, but generally occur 10-29 days after symptom onset.
- IgG responses have been detected as early as 6 days but typically occur approximately 19 days after symptoms.

Lyon GM. *N Engl J Med* 2014; 371, 2402-2409
McElroy AK. *Proc Natl Acad Sci U S A* 2015; 112, 4719-4724
The Beginning of my Ebola Story...

Hi Annie,

I would like to talk with you about 1) typing this individual’s blood (are there manual methods?), and 2) how we accomplish the plasmapheresis should we need it?

We think we may want this after all—patient getting sicker. Will be in touch.
Emergence of Convalescent Plasma

- As a result, physicians at the University of Nebraska (UNMC) and Emory University sought other immune therapies for the treatment of two additional patients with EVD medically evacuated to the US.
- In September, plasma was collected from a US survivor and transfused to a patient with EVD being treated at the UNMC.
- Ebola convalescent plasma (ECP) was subsequently used to treat multiple patients in the US and Europe with EVD and is currently in clinical trials in West Africa.
WHO Interim Guidance for the Use of Convalescent Plasma in EVD

DONOR CONSIDERATIONS

• Pre-donation testing should include:
  - ABO and RhD grouping
  - HIV, HBV, HCV, syphilis and other locally transmitted infections as applicable
  - Hemoglobin estimation (unless performed as part of the initial donor selection process)
  - Where possible: estimation of total Ebola antibodies and Ebola neutralizing antibodies

- Patients who have recovered from EVD and who have been discharged could be potential donors for CP from 28 days after discharge.
- The donor selection criteria used should be reviewed in light of the potentially life-saving impact of these specific donations.

Additional Donor Considerations

- Survivors of EVD have chronic sequelae including ocular deficits, hearing loss, hair loss, insomnia, arthralgias, and various constitutional symptoms
  - Findings from a recent retrospective cohort study noted that these sequelae persist for longer than 2 years post infection

- In addition, recent reports have demonstrated persistent viable EBOV in fluid from immune-privileged sites
  - Aqueous humor of the eye in a patient in recovery from EVD with acute panuveitis
    - Samples from conjunctivae and tears tested negative for EBOV suggesting no risk of spreading EVD through casual contact
  - Live EBOV can be isolated in seminal fluids of convalescent men for 82 days after symptom onset
    - Recent report of possible sexual transmission in a woman from Liberia who had unprotected sex with a man hospitalized for Ebola in October

http://mobile.nytimes.com/2015/05/08/health/weeks-after-his-recovery-ebola-lurked-in-a-doctors-eye.html?_r=0&referrer=
WHO Interim Guidance for the Use of Convalescent Plasma in EVD

RECIPIENT CONSIDERATIONS

- Only patients with confirmed EVD, preferably in its early stages, should be considered for CP transfusion.
- In the absence of evidence, 400–500 mL of CP in two doses of 200–250 mL each should be considered for adult patients.
- The need for repeat transfusion should be determined based on the clinical response and if feasible, on the level of neutralizing Ebola antibodies in the donor and the patient.

How We Obtained Convalescent Plasma for Treatment in EVD

1. Coordinated donor and collection

2. Contacted FDA and opened an emergency IND (eIND) using instructions on the FDA website:
   - eIND encompassed collection and transfusion of convalescent plasma
   - Provided FDA with the following information
     a. Brief clinical history and course of the recipient
     b. Treatment plan including plasma donor characteristics and procedure
     c. Monitoring
     d. Informed consent
     e. Alternative therapies

3. Contacted IRB and received emergency approval

4. Completed full eIND application
American Ebola patient got transfusion from cured doctor

Karen Weintraub and Liz Szabo, USA TODAY

Why Can't We Have More 'Magic' Blood for Ebola?

BY MAGGIE FOX

Dr Kent Brantly, the first American to return to the US from Liberia to be treated for Ebola, donated plasma to Nina Pham

New York Ebola patient Dr Craig Spencer receives blood transfusion from survivor Nancy Writebol as he enters the 'next phase' of deadly disease

Dallas nurse Amber Vinson thanks Dr. Kent Brantly, aid worker Nancy Writebol for plasma donations during her Ebola treatment - live video
Ebola Convalescent Plasma Transfusion

Case 3 in the US

- Previously healthy 51 year old male physician who was working in a hospital near Monrovia
- Medically evacuated to UNMC on day 7
- Plasma tested negative for EBOV RNA on days 22, 24, and 25
- Discharged on day 28

Kraft CS. Clin Infect Dis 2015; epub ahead of print
Ebola Convalescent Plasma Transfusion

Case 4 in the US

- Previously healthy 43 year old male physician who contracted EVD in Sierra Leone while treating patients in an ETU
- Medically evacuated to the Emory SCDU on day 4 of illness
- On days 37 and 38 of illness, blood was negative for EBOV RNA
- Discharged on illness day 44

Kraft CS. Clin Infect Dis 2015; epub ahead of print
Ebola Convalescent Plasma Transfusion

**Conclusions from Cases 3 and 4 in the US**

- The intensity of the supportive care provided to these repatriated physicians was clearly critical to the recovery of both patients.

- As in cases reported during this outbreak and previously, viral RNA levels correlated with disease severity and the appearance of adaptive immunity correlated with viral clearance and the beginnings of clinical recovery.

- However, it unknown whether the uncontrolled use of any specific experimental intervention modality or combinations thereof may have altered the clinical course of these EVD survivors.

- Nonetheless, it will be critical to be more prepared to undertake when this virus emerges again.
We have been contacted by ARC and had a conversation with FDA about a Compassionate Use IDE for treating plasma from recovered Ebola Virus (EBOV) patients with the INTERCEPT PI process for transfusion to patients with acute EBOV as passive immune therapy.

I would like to make contact with the clinician at Emory who treated these patients to see if he can share information regarding NAT assays for EBOV and Ig and IgM titers in their plasma after recovery. As you may know the first patient donated plasma for transfusion into the third patient without pathogen inactivation treatment. FDA is interested in this protocol that would allow potential creation of a plasma stock for passive immune therapy during acute EBOV infection. There is some limited clinical data indicating that this may be a useful therapy; but a study to collect more data would be useful.

I would appreciate any information that you can provide, and if you are willing to provide an introduction for me to that would ease the pathway. I suspect that you may know him through your clinical activities.

Thanks for any assistance you can render –

Best - Larry

Laurence Corash, MD
Chief Medical and Scientific Officer
Senior Vice President Medical Affairs
Cerus Corporation

Sent: Thursday, September 11, 2014 12:54 AM
To: Winkler, Anne M.
Subject: FW: Ebola Virus Immune Plasma

What do you think about this?
Ebola Convalescent Plasma Bank

- The goal is to collect, pathogen inactivate, characterize, and store plasma from survivors of EVD to create a national inventory of an unlicensed biologic product

- ECP Bank
  - Safe intervention with low side effect profile
  - Currently one of two mechanisms for collecting ECP in US
    - Prior to IDE, 10 liters collected and transfused from 5 donors
    - Following initiation of IDE, 7 liters banked
Ebola Convalescent Plasma Bank

• Over the last year, we have developed the infrastructure to collect ECP
  – Mechanism includes a Cerus sponsored investigational device exemption (IDE) that two of four biocontainment units will use to provide banked ECP to patients with EVD
• A Prospective, Open Label, Phase 1 Safety Study of Passive Immune Therapy During Acute Ebola Virus Infection Using Transfusion of INTERCEPT Plasma Prepared From Volunteer Donors Who Have Recovered From Ebola Virus Infection
  – ClinicalTrials.gov Identifier: NCT02295501
Ebola Convalescent Plasma Bank

• Cerus sponsored IDE
  – Collection of plasma using apheresis
  – Pathogen inactivation using the INTERCEPT Blood System for plasma
    • Important step because all donors do not meet established criteria for blood donation
  – Laboratory Testing
    • ABO isohemagglutinin titers
    • HLA antibody screening
    • Infectious disease screening
    • Ebola antibody titer and neutralizing antibody testing
  – Storage in preparation for distribution as needed
  – Transfusion of ECP to US patients with acute EVD
EBOLA VIRUS OUTBREAK

Continuing coverage of the ebola outbreak in Africa and its effects in the U.S. and around the world.

Magic Blood? Emory's Ebola Plasma Bank

BY MAGGIE FOX

Photo Courtesy of Donna Martin. Used with Permission from Will Pooley
Ebola Convalescent Plasma Bank

Treatment and Source Material

• By banking characterized ECP, we have the ability to quickly facilitate the distribution of this product

• ECP could also be used as source material for
  – Development of lyophilized plasma for long-term storage and distribution
    – INTERCEPT-treated plasma is currently freeze-dried by the French and is used under IND by the US Army Special Forces
  – Manufacturing hyperimmune immunoglobulin
  – Characterization of assays required to determine efficacy of ECP
    • Coordination and standardization of Ebola anti-glycoprotein titer and neutralization assays in collaboration with the WHO Ebola Antibody Assay Working Group
Ebola Convalescent Plasma Bank

Translational Research

• Further characterize the humoral response to Zaire ebolavirus
  – Data from Sudan ebolavirus outbreaks has demonstrated that half of survivors have detectable neutralizing antibodies
    • Neutralizing capability has persisted in specific individuals for extended periods of time even up to 10 years post-infection

• Return to pre-clinical studies to determine efficacy of ECP in animal models
Conclusions

• As the current outbreak wanes, it is unlikely that additional trials with mortality endpoints that had been proposed will be launched or reach their enrollment.

• As a result, we will likely know little about the efficacy of any experimental agent by the time the dust settles from the current outbreak.

• Nonetheless, it will be critical to be more prepared to undertake rigorous clinical and translational research in antiviral therapeutics when this virus emerges again.

• A central element will be the need to continue to support the research required to have well characterized vaccine and drug candidates ready before we are challenged by the next outbreak.
Thank you for your attention