Intervention Options against Ebola

Experience and Outlook

Micha Nübling, 20 May 2015
Ebola epidemiological curve

Guinea

Sierra Leone

Liberia
Week 13.05.2015: 9 cases
The World Health Organization's response to Ebola virus disease (EVD) comprises four elements:

- Response in affected countries
- Preparedness in non-affected countries
- Research and Development for health products
- Health systems recovery/reconstruction
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- Response in affected countries
- Preparedness in non-affected countries
- Research and Development for health products
- Health systems recovery/reconstruction
Accelerating access to vaccines and therapeutics is a high priority

In parallel…

Development

Testing

Licensure

Plan for use
Gathering knowledge

- Since August 2014, series of consultations with key international experts and stakeholders to identify potential preventive, diagnostic or therapeutic solutions for Ebola

- Based on concerted expert advice, WHO has prioritized a number of products for further investigation through human testing:
  - two candidate vaccines
  - a shortlist of antiviral drugs
  - Ebola diagnostics
  - convalescent whole blood and plasma
Gathering knowledge

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Gathering knowledge

Candidate Vaccines

100% efficacy in non-human primates
but not tested in humans so far

- Recombinant vesicular stomatitis virus (rVSV-ZEBOV)
  replicating recombinant virus

- Chimpanzee adenovirus serotype 3 (ChAD3-ZEBOV)
  non-replicating recombinant virus
ChAd3-ZEBOV

cAd3 genome

\[\text{E}1\quad\text{E}4\]

E1 replaced with EBOV GP gene inserts

\[\text{EBOV GP}\]

\[\text{GP}_1\quad\text{GP}_2\]

cAd3–EBOV

E4 deleted

rVSV-ZEBOV

VSV wild-type

\[\text{N}\quad\text{P}\quad\text{M}\quad\text{G}\quad\text{L}\]

Deletion of fusogenic VSV-G protein with substitution of Ebolavirus Zaire–strain Kikwit envelope protein

BPSC1001

\[\text{N}\quad\text{P}\quad\text{M}\quad\text{EBOV GP}\quad\text{L}\]

R&D for potential vaccines, therapies and diagnostics for Ebola
Update

16 January 2015
Gathering knowledge

Joint efforts by international consortia to obtain authorisation of clinical trials in short time frame

- joint assessments, work sharing
  - FDA / EMA / WHO / NRAs from different countries, including African Ethic commissions

Study sites in the US, Europe, Africa

Authorisation of Phase 1 – 3 trials
ChAD3-ZEBOV

Glaxo Smith Kline, U.S. Nat Inst Allergy Infect Dis

Safety profile in humans of related ChAD experimental vaccines:

no safety concerns
ChAd3-ZEBOV

GSK, NIAID (USA)

A Monovalent Chimpanzee Adenovirus Ebola Vaccine — Preliminary Report

ChAD3-ZEBOV

Phase 1

Antibody, cytotoxic T-cells in humans < in macaques efficacy studies

Ab gp binding activity: as rec VSV vaccine

monovalent vaccine sufficient (MVA vector boost)
NewLink Genetics, PHA Canada

postexposure (needle-stick) treatment in a laboratory worker

Preliminary Communication

Emergency Postexposure Vaccination With Vesicular Stomatitis Virus-Vectored Ebola Vaccine After Needlestick

Lilin Lai, MD; Richard Davey, MD; Allison Beck, MPAS; Yongxian Xu, MD; Anthony F. Suffredini, MD; Tara Palmore, MD; Sarah Kabbani, MD; Susan Rogers, RPh; Gary Kobinger, PhD; Judie Allmont, PhD; Charles J. Link Jr, MD; Lewis Rubinson, MD; Ute Ströher, PhD; Mark Wolcott, PhD; William Dorman, BS; Timothy M. Uyeki, MD; Heinz Feldmann, MD, PhD; H. Clifford Lane, MD; Mark J. Mulligan, MD

Published online March 5, 2015.
rVSV-ZEBOV

Phase 1/2 trials: Europe / Africa

transient viral replication (3 d)
short viraemia
(“arthritic”)

antibodies: gp binding
neutralizing: dose dep

Phase 1 Trials of rVSV Ebola Vaccine in Africa and Europe — Preliminary Report


The NEW ENGLAND JOURNAL of MEDICINE

World Health Organization
rVSV-ZEBOV

Phase 3, April 2015

frontline workers
ring vaccination in Guinea (23.03.2015)

Contribution to current decline of numbers?

Proof for efficacy?
Gathering knowledge

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Therapeutics

- >100 drugs proposed to WHO: “potential antiEBOV activity”
- Prioritization according to data from clinical trials
  - Category A- D according to information on Ebola-related efficacy in humans from clinical trials
- Table on WHO continuously updated
- Deprioritization
- Prevention of competition for patients for clinical trials
**Therapeutics**

- **Favipiravir**: viral RNA polymerase inhibitor, NHP efficacy: 2 log reduction in viremia (Toyama Chemical, Japan)
- **TKM-100802**: NHP efficacy 30 min post challenge (Tekimira pharmaceuticals; BC, Canada),
- **Zmapp**: NHP efficacy 5 days after challenge (MappBio, USA)
- **AVI 7537**: phosphoramidate oligonucleotide, antiVP24 (Sarepta Therapeutics, MA, USA)
- **Brincidofovir** (Chimerix; NC, USA)
- **BCX4430**: adenosine analogue (BioCryst, NC, USA)
- **Interferons**
Currently ongoing clinical trials

- **TKM-100802**: lipid nanoparticle delivering small interfering RNA (siRNA), NHP efficacy 30 min post challenge (Tekimira pharmaceuticals; BC, Canada)

- **Zmapp**: Cocktail of three monoclonal antibodies produced in tobacco plants, NHP efficacy 5 days after challenge (MappBio, USA)
Gathering knowledge

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- Based on concerted expert advice, WHO has prioritized a number of products for further investigation through human testing:
  - two candidate vaccines
  - a shortlist of antiviral drugs
  - **Ebola diagnostics**
  - convalescent whole blood and plasma
Ebola diagnostics

- Diagnosis of symptomatic patients; therapy monitoring
  - NAT assays
  - Antigen tests

- Screening of contact persons
  - NAT assays

- Vaccine trials
  - antiEBOV-gp titre
  - EBOV neutralisation

- Characterization of convalescent plasma / blood
  - EBOV antibody patterns
  - EBOV neutralising antibodies
WHO emergency use assessment and listing procedure (EUAL)

(IVD prequalification team)

- Review of assay design; performance data, if available
- Review of QMS
- Antigen RDT: independent field study: basic assay features
- NAT: independent lab evaluation: limit of detection
Ebola diagnostics

Currently listed (WHO EUAL)

- ReEBOV™ Antigen Rapid Test Kit (Corgenix)

- RealStar® Filovirus Screen RT-PCR Kit 1.0 (Altona)

- Liferiver™ - Ebola Virus (EBOV) Real Time RT-PCR Kit (Shanghai ZJ BioTech)

- Xpert® Ebola Assay (Cepheid AB)

- ............
Ebola diagnostics

WHO guidance on selection and use of Ebola IVDs

- Setting (remote testing, reference lab)
- Confirmation of test results
- PPV, NPV
Ebola diagnostics

Standardization (NIBSC)

- NATs

- Antibody tests
  - vaccine trials
  - convalescent plasma

- Antigen tests

Materials available

- recomb constructs
  - lentiviral
  - flu

- sera / plasma
  - transchromosomomal (bovine)
  - convalescent
  - vaccinees

- ..............
Gathering knowledge

There is consensus that the use of whole blood and convalescent blood serums needs to be considered as a matter of priority.

( WHO meeting 4/5 Sep 2014 )
Convalescent Whole Blood (CWB) and Plasma CP

- Effective in treatment of infections
  - Diphteria, Tetanus serum therapy (Behring, 1890)
  - Influenza H1N1
  - CMV
  - Hantavirus (Vial, 2014)
  - Junin virus, AHF (Maiztegui, 1979)
  - Ebola (?): CP treatment of 1 patient (Edmond, 1977)
    CWB treatment of 8 patients (Mupapa, 1999)
WHO Blood Regulators Network (BRN)

Position Paper on Collection and Use of Convalescent Plasma or Serum as an Element in Filovirus Outbreak Response*

August 14, 2014

- Potential suitability of CP/CWB
  Clinical use of Ebola CP/CWB investigational
  Characterization of CP/CWB: neutralizing Abs?
  Virus inactivation of CP

- Regulatory Agencies
  screening of donors
  design of trials
  evaluation

- Need for controlled studies
  pilot studies in humans
  NHP models
  negative human plasma / whole blood as comparator
Use of Convalescent Whole Blood or Plasma Collected from Patients Recovered from Ebola Virus Disease for Transfusion, as an Empirical Treatment during Outbreaks

WHO advice on

- CWB/CP donors
- Products
- CWB/CP recipients
Use of Convalescent Whole Blood or Plasma Collected from Patients Recovered from Ebola Virus Disease for Transfusion, as an Empirical Treatment during Outbreaks

**CWB/CP donors**

- 28 days after discharge from ETU
- 2 x Ebola PCR neg, ≥ 2 days apart
- TTI screening neg, ABO, RhD

  apheresis plasma: 2 weeks interdonation
  whole blood: 12 – 16 weeks interdonation

informed consent (Annex)
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Clinical Aspects of Ebola Virus Disease

Figure 2. Ebola virus shedding in body fluids. Colors=PCR positive. Bars=culture positive. Source: Pierre Rollin/CDC
Use of Convalescent Whole Blood or Plasma Collected from Patients Recovered from Ebola Virus Disease for Transfusion, as an Empirical Treatment during Outbreaks

Products (CWB/CP)

- Storage
- Traceability
- Back-up specimens

CWB/CP recipients

- preferably early stage of disease
- administration of CWB/CP
- patient monitoring, including viral load
- informed consent (Annex)
# Blood Products Clinical Trials

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Organization / Location</th>
<th>Description</th>
<th>Type of Blood Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liberia</td>
<td>Government US (Clin RM/BMGF)</td>
<td>few patients use of “excess” plasma?</td>
<td>Whole blood Plasma</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>Government SL/UK/US</td>
<td>&gt;50 patients, data eval?</td>
<td>Whole Blood Plasma</td>
</tr>
<tr>
<td>Guinea</td>
<td>Guinea/Belgium/UK/France</td>
<td>Running started 02/15, 86 patients</td>
<td>Plasma</td>
</tr>
</tbody>
</table>

Expatriated patients – receiving convalescent plasma
Experiences

- Clinical trials
  - Infrastructure
  - Logistical issues
  - Agreement of local authorities
  - no control group
  - improvement of clinical care
  - patients enter ETUs at earlier stage of disease (ct-values)
Blood Products Clinical Trials

Experiences

- Clinical trials
  - CWB donors (Sierra Leone)
    60 / 200 candidates suitable for donation (health conditions)
  - Declining Ebola epidemiology
    collection and storage of CP
    immunoglobulin fractionation?
Conceptual Framework for Health Sector Response, Recovery & Resilience from the Ebola Crisis

Response

‘Getting to Zero’

6-12 months

Recovery Priorities

Restore trust in health services

Ensure preparedness for health shocks

Define an essential service package

Enhance capacity to deliver service

Increase access to essential services

Development

2015

5-10 years

‘Health Systems Development’
Turning crisis into opportunity

Blood collection systems in Ebola-affected countries

Convalescent plasma: spotlight on blood system infrastructures

Ebola affected countries with rudimentary blood system infrastructure before Ebola

No separation of whole blood into components

- 90% replacement / paid donations
- 30% maternal deaths due to blood shortage
- many child deaths due to anemia caused by malaria

Blood collection stopped completely with Ebola crisis

25-27 Feb 2015, 2-4 June 2015
Meetings on developing plan to strengthen the blood systems in Ebola-affected countries

Country-specific proposals for recovery and development of blood collection systems
“The cloud of Ebola may have a silver lining by bringing attention and support to blood services when they have never previously had sufficiently high priority.”

Dr Samuel H. Baker, Programme Manager, National Safe Blood Transfusion Service, Sierra Leone
Thanks to…

Dr David Wood (WHO)
WHO document on key considerations for effective community engagement in blood donation for compassionate use and clinical trials

Prevention of stigmatisation of EVD survivors

Draft model to enable national health authorities, blood transfusion services and trial investigators to effectively engage with communities to prepare EVD survivors and the communities for blood donation and the clinical trials

Aims to help to ensure informed participation of survivors and communities and avoid the additional pressure and anxiety inappropriate and/or insufficient community engagement can place to already vulnerable groups.