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The Use of Ebola Convalescent Plasma to Treat Ebola Virus Disease in Resource-Constrained Settings: A Perspective From the Field

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The clinical evaluation of convalescent plasma (CP) for the treatment of Ebola virus disease (EVD) in the current outbreak, predominantly affecting Guinea, Sierra Leone, and Liberia, was prioritized by the World Health Organization in September 2014. In each of these countries, nonrandomized comparative clinical trials were initiated. The Ebola-Tx trial in Conakry, Guinea, enrolled 102 patients by 7 July 2015; no severe adverse reactions were noted. The Ebola-CP trial in Sierra Leone and the EVD001 trial in Liberia have included few patients. Although no efficacy data are available yet, current field experience supports the safety, acceptability, and feasibility of CP as EVD treatment. Longer-term follow-up as well as data from nontrial settings and evidence on the scalability of the intervention are required. CP sourced from within the outbreak is the most readily available source of anti-EVD antibodies. Until the advent of effective antivirals or monoclonal antibodies, CP merits further evaluation.

Keywords. convalescent plasma; clinical trial; Ebola; therapy; Guinea.

Convalescent blood or plasma transfusion has been used in clinical settings for >100 years [1]. Until the advent of antibiotic therapy, it was widely used for a range of bacterial and viral diseases. A recent meta-analysis suggests that it could have contributed to an absolute reduction in mortality of around 20% during the 1918 influenza epidemic [2]. At present, hyperimmune globulin, manufactured from convalescent donors' plasma, is still employed as prophylaxis or treatment for certain infectious diseases (eg, measles, diphtheria, polio, hepatitis A and B) [3]. Passive antibody therapy is not a new intervention but a widely tested, safe, and proven prophylactic and therapeutic intervention.

Over the last 10 years, convalescent plasma (CP) has been explored for the treatment of viral severe acute respiratory infections such as severe acute respiratory syndrome and (avian) influenza. A recent meta-analysis identified 32 studies that indicated, overall, a 75% reduced risk in the odds of mortality, particularly if CP was administered early after symptom onset [4, 5]. CP is currently being considered as treatment for Middle East respiratory syndrome [6].

For hemorrhagic fevers, well-documented, relatively recent experience stems from a randomized controlled trial comparing CP (1 single unit of 500 mL) with normal plasma against Argentine hemorrhagic fever [7]. Mortality was 1.1% among the 91 patients who received CP compared to 16.5% in the 97 patients treated with normal plasma. Of interest, a delayed neurological condition was observed in some patients after CP therapy, occurring several weeks after apparent cure. CP has also been explored against the hemorrhagic disease Lassa fever, with conflicting results [8–11].

The World Health Organization (WHO) guidelines recommend both convalescent whole blood (CWB) and CP for use against Ebola virus disease (EVD) [12]. During EVD outbreaks, both are local and readily available sources of anti-EVD antibodies. Blood transfusion is routinely done in all 3 high-transmission countries involved in the current EVD outbreak; however, plasma has numerous advantages in these settings. Using apheresis, a single donor can give substantially more CP, up to 10 mL/kg every 2 weeks, compared with 1 unit of 450 mL whole blood (approximately 250 mL plasma) every 3–4 months for CWB; hence, more patients can be treated. CP can be given intravenously over a much shorter time period (30 minutes vs 3–4 hours) and hence is less demanding for health-care teams in Ebola treatment centers. The pathogen inactivation step during CP production increases the safety of the intervention. CP transfusion is also safer with fewer transfusion reactions; CP needs to be ABO compatible, but there is no need for bedside cross-matching [13]. Additionally, CP can be stored for much longer periods.

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Hyperimmune globulin has advantages compared with CWB and CP, as it is a concentrated and purified product [14]. However, this product is presently not available against EVD, and hence it has not been evaluated in the current Ebola outbreak. Nevertheless, it represents an interesting longer-term potential therapy, especially if the ongoing studies suggest efficacy of CP. Recombinant monoclonal antibodies are currently being evaluated in Sierra Leone and Guinea [15], but will not be discussed in detail given this article's focus on convalescent blood products.

EFFICACY

Animal Studies

The successful use of ZMapp (an antibody cocktail comprising 3 Ebola virus-specific recombinant monoclonal antibodies) for treatment of EVD in non-human primate models, even when administration is delayed until 5 days after a supralethal viral challenge, provides proof of concept of antibody-based therapy for EVD [16]. Similarly, the use of immunoglobulin fractions from convalescent animals is effective for treating EVD in non-human primates [17]. Earlier treatment attempts with monoclonal antibodies or immunoglobulins might have failed because antibody concentrations were too low, antibodies had too narrow a spectrum (eg, 1 monoclonal only), or because treatment was not given repeatedly (ZMapp is given 3 times [days 0, 3, 6]).

Early CWB studies with nonhuman primates failed to demonstrate efficacy when rhesus macaques were transfused immediately after challenge [18]. There are no animal studies with convalescent plasma against EVD. Key questions include whether antibody titers are high enough in CP and CWB to be effective, and if 1 single transfusion, as per current WHO guidelines, is sufficient. The exact kinetics of neutralizing antibodies in convalescent donors and variation between individuals are currently not well described.

Clinical Data

Clinical data are limited. The most important study on CWB in EVD reported on 8 individuals treated during the Kikwit outbreak in 1995; 7 survived [19]. However, this was an uncontrolled small study, with patients enrolled relatively late after onset of symptoms. Moreover, several factors beyond an antibody-related effect could have contributed to the improved survival, such as improved hydration or the administration of other blood components such as clotting factors. Moreover, a subsequent analysis after adjustment for age, sex, and number of days since onset of symptoms showed no survival benefit of CWB [20]. One well-documented case occurred in 1976 when a laboratory technician survived EVD after receiving 2 plasma transfusions combined with interferon injections [21].

Several EVD patients (mainly expatriates) have been treated with CWB, CP, or recombinant monoclonal antibodies during

the current outbreak [22–26]. However, most of these patients received multiple anti-EVD interventions and high-quality supportive care, so it is not possible to assess the efficacy, if any, of passive antibody transfer.

In conclusion, whereas the data on ZMapp provide proof of concept, clinical data on and experience with convalescent blood products for the treatment of EVD are very limited. Consequently, WHO prioritized the need to evaluate CP in clinical trials, with the aim to determine its efficacy, safety, and feasibility. Notably, these interventions can be organized by harnessing or increasing existing national capacities quickly within the affected countries, without the complications or limitations associated with shipping commercial products, which are often in limited supply.

Clinical Trials on CP in the 2014–2015 EVD Outbreak in West Africa

An overview of clinical trials is provided in Table 1. The Ebola-Tx trial, in Conakry, Guinea, is designed to assess the feasibility, safety, and efficacy of CP against EVD [27]. Survival at 14 days after transfusion of patients treated with CP plus supportive care will be compared to that of patients receiving supportive care alone, in an open-label phase 2/3, nonrandomized comparative study. All eligible and consenting patients of any age with confirmed EVD (including pregnant women) are enrolled; exclusion criteria are limited to contraindications for CP or patients arriving in a close to terminal condition. Available ABO compatible plasma is given, within 48 hours after diagnosis, on a first-come, first-served basis. Patients for whom there is no available compatible plasma are enrolled as concurrent controls, complemented with historical controls. The first plasma collection started on 9 February 2015, followed by the first CP administration on 19 February 2015. As of 7 July 2015, 102 patients have been recruited. The main analysis is planned when a cohort of 130 CP-treated patients have reached day 14 posttransfusion. Due to the fluctuating number of new patients and the decline of the outbreak in Guinea, it is difficult to estimate when this will happen.

The Ebola-CP consortium in Sierra Leone, which emerged out of the Ebola-Tx initiative, is conducting a parallel study in Freetown using a similar protocol, CRF, and data management. The first patient was recruited 19 March 2015 as a control (no CP given); due to the declining outbreak in Sierra Leone, as of 23 July 2015, 3 patients have received CP.

The EVD001 trial is a phase 1/2 pilot study with viral load changes as the primary outcome [28]. Children and pregnant women are excluded. The study started in Monrovia in November 2014 but subsequently closed due to the decline in caseload. A total of 4 CP-treated patients and 2 controls were included.

The Ebola medical treatment team in the 34th Regiment Hospital Freetown, Sierra Leone, has been administering CWB, as per WHO guidance, for compassionate use from December 2014 to March 2015 (<http://awoko.org/2014/12/09/sierra-leone-news-convalescent-blood-treatment-started/>). A total of 52 patients opted for CWB transfusion with 24 included

Table 1. Overview of Clinical Trials Conducted During the 2014–2015 Ebola Virus Disease Outbreak in West Africa

| Characteristic/Feature | Ebola-Tx | Ebola-CP | EVD001 |
|----------------------------|---|--|--|
| Funder | European Union | Wellcome Trust | Bill & Melinda Gates Foundation |
| Sponsor | Institute of Tropical Medicine Antwerp | University of Liverpool | ClinicalRM |
| Study site | Conakry, Guinea | Freetown, Sierra Leone | Monrovia, Liberia |
| Start date | February 2015 | April 2015 | November 2014 |
| Donor selection criteria | PCR-confirmed EVD >90 d after discharged cured (laboratory confirmed) | PCR-confirmed EVD >28 d after discharged cured | PCR-confirmed EVD >28 d after discharged cured; >60 d after EVD onset |
| Donor testing (infections) | HIV, HBV, HCV, syphilis | HIV, HBV, HCV, syphilis; EVD PCR (plasma), antibodies (ELISA) | HIV, HBV, HCV, syphilis EVD PCR (plasma), antibodies (ELISA) |
| Plasma collection | Apheresis & pathogen reduction (amotosalen) | Apheresis & pathogen reduction (amotosalen) | Apheresis & pathogen reduction (amotosalen) |
| Study population | Confirmed EVD—all ages including pregnant women | Confirmed EVD—all ages including pregnant women | Confirmed EVD—adults only (>18 y) |
| Study design/phase | Phase 2/3 | Phase 2/3 | Phase 1/2 pilot study |
| Intervention | Two units (200–250 mL each, different donors) given consecutively | One unit of 500 mL originating from 1 single donor | Two units (100 mL each, different donors) repeated at 48 h as indicated |
| Primary outcome | Survival at 14 d | Survival at 14 d | Change in VL and EV antibody levels |
| Secondary outcomes | (1) survival at 30 d; (2) serious adverse reactions; (3) change in VL; (4) safety risks in health workers; (5) risk factors for mortality | (1) survival at 30 d; (2) serious adverse reactions; (3) VL and EV IgG antibody levels over time; (4) safety risks in health workers | (1) survival at discharge; (2) safety; (3) VL and EV IgG antibody levels over time |

Abbreviations: CP, convalescent plasma; EV, Ebola virus; EVD, Ebola virus disease; ELISA, enzyme-linked immunosorbent assay; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgG, immunoglobulin G; PCR, polymerase chain reaction; VL, viral load.

as controls. None of the ongoing clinical studies have reported findings.

Designing trials, and recruiting patients, to evaluate CWB and CP has been challenging. Only Ebola-Tx has achieved a relatively high sample size (>80 CP-treated patients). The design that would provide the best evaluation would be a randomized trial in which one or other intervention would be compared with control patients not receiving the intervention. However, such randomized designs have proved unacceptable in the volatile settings of the current Ebola outbreak, and researchers have at the early stages resorted to nonrandomized study designs [29]. All CP trials were designed to include concurrent control patients. For example, in the Ebola-Tx trial, controls were to be patients presenting when no ABO-compatible plasma was available. However, when the trial started, the supply of CP increased significantly and the number of patients decreased, resulting in sufficient supply of CP to treat nearly all patients. Consequently, it will compare the mortality of treated patients with that of historical controls, with the inherent possibility of biased comparisons. Key concerns in all trials regarded potential confounding factors including variations in patient characteristics, Ebola virulence on presentation, and differences in standards of supportive care over time. For example, the systematic placement of intravenous access lines in patients for CP treatment could encourage more aggressive intravenous hydration during the trial period. How easy it will be to interpret the results of the trials will depend, to a large extent, on the size of the mortality reduction, if any, associated with the intervention.

SAFETY

Plasma transfusion is considered a relatively safe procedure, particularly if pathogen reduction is done. However, for use as a treatment of EVD, there are additional considerations. Safe production, storage, and distribution need to be organized in the affected countries. Plasmapheresis technology needs to be available or introduced, including quality-assured testing for transfusion-transmissible infections and an effective cold chain, all of which have been major challenges in the currently affected West African countries. Although standards for blood group typing are clearly defined in the national guidelines, errors can result from field realities, such as lack of resources, supervision, and poorly incentivized staff. Additionally, weak systems of documentation can lead to poor or mistaken identification.

The infection control environment of Ebola treatment centers brings with it difficult operational challenges, both for care of patients and, in particular, for the implementation of clinical research. Short and intermittent patient contact by staff in protective clothing, with potentially confused patients, is the norm. Therefore, mistakes are more likely to occur, such as in patient identification, labeling of blood tubes, and request forms during sample collection and packaging. Moreover, introducing the procedure for blood group typing into already overloaded EVD diagnostic laboratories might engender additional errors. This can potentially increase the risks of adverse reactions due to preanalytical, analytical, or postanalytical errors. These errors could potentially lead to severe reactions if

Table 2. Advantages and Disadvantages of Different Sources of Antibodies Against Ebola Virus Disease

| Characteristic/Feature | Convalescent Whole Blood | Convalescent Plasma | Hyperimmune Globulins ^a | Recombinant Monoclonal Antibodies |
|--|---|---|---|--|
| Availability | Survivors in affected countries can act as source | Survivors in affected countries can act as source | Currently not available, requires high amounts of CP or production in animals | Limited; potential for more efficient production methods |
| Accessibility in affected low-income countries | Produced within and by the affected countries | Produced within and by the affected countries | Not clear how it will be marketed and how prioritization will be decided | Not clear how it will be marketed and how prioritization will be decided |
| Collection/production | 1 donation/3–4 mo (10 mL/kg) | 1 donation/2 wk (10 mL/kg) | One production plant in Africa | US (1) and Chinese (1) company |
| Storage | >1 mo (2°C–6°C) | 3 y (–30°C) | 2–3 y (4°C) | Long-term (–20°C) |
| Administration | IV (4 h) | IV (20–40 min) | IV (variable, usually <1 hour) or IM | IV (6–12 h) or subcutaneous |
| Potential side effects | +++(+) ^b | +(+) ^b | + ^b | +++(?) ^b |
| Risk with ABO incompatibility | ++++ ^b | + ^b | NA | NA |
| Costs/affordability | + ^b | ++ ^b | +++ ^b | ++++ ^b |
| Acceptability in EVD context | Well-known procedure Current data suggest reasonable donor acceptability | New procedure; Current data suggest reasonable donor acceptability | Presumably good | Presumably good |
| Activity against circulating virus | CWB produced during outbreak likely effective | CP produced during outbreak likely effective | Activity to be shown against viruses causing new outbreaks | Activity to be shown against viruses causing new outbreaks |
| Production time | Short (<1 d) once donors identified | Short (days) once donors identified | Months | Months |

Abbreviations: CP, convalescent plasma; CWB, convalescent whole blood; EVD, Ebola virus disease; IM, intramuscular; IV, intravenous; NA, not applicable.

^a Most efforts currently focused on human sources of antibodies, but animal production is under exploration as well.

^b +: Very low; ++: Low; +++: Moderate; +++(+): Moderate to high; ++++: High; (?): Substantial uncertainty given limited clinical experience.

ABO-incompatible plasma with high titers of hemolysins were administered.

The ability to monitor patients for and to react to severe, acute adverse reactions is clearly limited by the environment of many Ebola treatment centers. Some (severe) transfusion reactions might erroneously be attributed to EVD [29,30]. For instance, respiratory difficulties, often seen during EVD, might be due to transfusion-related acute lung injury. Patient management options for adverse events may also be limited.

It has been suggested for a number of viruses, including Ebola, that the transfer of antibodies might enhance pathogenicity, possibly by antibody-enhanced cell entry [31]. Although more recent studies have suggested that this is unlikely to have clinical significance, it still requires special attention and careful evaluation when employing CP, regardless of whether it is for clinical trials or compassionate use [32].

No severe adverse reactions or safety risks for healthcare staff have been noted in the Ebola-Tx trial by 7 July 2015. While this suggests that CP can be employed safely for EVD treatment, the use of such treatment, if found efficacious, should be evaluated in noncontrolled settings before introducing it as a standard of care in public health facilities.

FEASIBILITY AND ACCEPTABILITY

The quality of blood transfusion services in many West African countries is generally poor, and in many countries, plasma production is not routinely performed [33]. During the EVD out-

break, effective plasmapheresis teams were assembled relatively quickly, mainly in mobile plasma units or “plasma mobiles” (<http://www.gatesfoundation.org/Media-Center/Press-Releases/2014/11/Support-to-Ebola-Affected-Countries-Announcement>), and national blood transfusion teams trained. This was made possible by the substantial funding made available through international research consortia. As the situation dictated an emergency response, the plasmapheresis material introduced for use in the present trials is unlikely to be an optimal choice for the concerned national transfusion centers. A transition to simpler, nonautomated systems might be indicated. Furthermore, pathogen reduction is an expensive procedure and unlikely to be a priority for resource-constrained settings, where the prerogative is the provision of safe basic blood banking services. The experience of the present trials, which has identified the need to further improve the overall quality of blood banking centers in all 3 countries, should result in longer-term capacity-building projects once the outbreak is contained.

The use of convalescent blood products is further complicated by the requirement to carefully and properly manage the engagement of Ebola survivors, who are often stigmatized in their communities. In many West African countries there is reticence toward blood collection, donation, and transfusion, based on superstitions and beliefs in the community [34,35]. Experience during the 2014–2015 outbreak suggests that if there are appropriate community consultations and discussions, there is a reasonable acceptability among plasma donors, surviving patients,

and their family members, at least in the short term. However, a better understanding of plasma donor motivation is required to ascertain whether possible degrees of coercion have occurred. In all 3 high-transmission countries, EVD survivors have organized themselves into survivor associations. Although this has probably substantially eased donor mobilization, more in-depth assessments of their potential role are merited.

Other key concerns include confidentiality and privacy, especially if members of the survivors association are involved in the recruitment process. Additionally, confronting individuals recently recovered from EVD with positive serological tests for other infections can have negative consequences. Lack of free access to care for infections such as hepatitis B and C further compounds the situation [36]. Hence, longer follow-up and more in-depth anthropological assessments among plasma donors and patients are required to further document the acceptability and feasibility of CP as EVD treatment. It has been suggested that involving survivors as donors in a potentially life-saving treatment could support their social reintegration and reduce stigma, but evidence for this is currently lacking.

SCALABILITY

Although hopefully there will not be another Ebola outbreak on the scale of the present one, it would be possible to stockpile plasma for emergency use. There are currently >15 000 Ebola survivors in the 3 high-transmission countries. A single donor, donating 600 mL every 2 weeks, could provide sufficient plasma to treat around 35 patients. With 500 regular donors (approximately 3% of the potential total), a total of 17 500 treatments would potentially be available. Prequalification of donors with high titers of neutralizing antibodies would make the process most efficient. Such scaling up of CP would require either decentralized plasma production or safe transport and storage of CP from a central location to more remote areas.

Blood transfusion regulations recommend that people who received a blood transfusion should not be permitted to donate blood for 12 months after the date of transfusion, mainly related to the risk of pathogen transmission. Applying this to EVD survivors following CP treatment would seriously reduce the donor pool. However, if CP is shown to have a substantial effect, the benefits of using such patients as donors would probably outweigh potential risks. It should also be confirmed that CP-treated patients develop sufficient level of neutralizing antibodies against the virus, particularly if treated early in the disease course.

The logical next step is to produce hyperimmune globulins from the donated plasma, and several initiatives are focusing on this. As purified and concentrated products, hyperimmune globulins are generally considered to be safer and with higher, less variable antibody titers than CP (Table 2). They can also be stored for prolonged periods. Animal production of hyperimmune globulins is also under exploration ([\[techcom/technologie/technology/\]\(http://www.faben.techcom/technologie/technology/\)\). Pending the building up of such expertise within Africa, production could be outsourced.](http://www.faben</p></div><div data-bbox=)

CONCLUSIONS

Current field experience supports the use of CP against EVD as acceptable, feasible, and safe. Efficacy data are pending. In consideration of the study design limitations described in this article, these trials may not yield definitive data on the extent to which such treatment reduces case fatality rates. However, it is expected that they will, at minimum, provide some indication of the utility of CP and the challenges in delivering such treatment, in future trials. Additional research on CP, hyperimmune globulins, and monoclonal antibodies in animal and clinical studies is required to identify the optimal treatment regimen and better understand the mechanism of action.

Long-term studies are also required to document better the feasibility and acceptability of CP donation outside of a research setting, to assess the willingness of survivors to become CP donors and to identify any negative immunological, medical, or psychosocial effects of repeated CP donations. Longer follow-up of CP treated patients is also indicated to detect late adverse events.

Although hyperimmune globulins and recombinant monoclonal antibodies have several advantages, the use of CP sourced from within an outbreak is arguably the most readily available source of anti-EVD antibodies and will always have the advantage that it is likely to be active against the circulating strain. In each new outbreak, available hyperimmune globulins or monoclonal antibodies will first have to be evaluated against the causative strain and possibly followed by the production of a new product, all of which takes time. Until the advent of potent, safe, affordable, and effective antivirals, and the development of effective vaccines, the use of convalescent blood products should remain part of the potential response to EVD.

Notes

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