Convalescent Serum Therapy
A DISSENTING VIEWPOINT

ANDREW HAWKINS

The acute outbreak of the Ebola virus in West Africa has been a disturbing event.[1] Ebola is a pathogen for which there is no known treatment.[2] Healthcare professionals are left without adequate clinical infrastructure to combat this high-mortality disease. In response to this reality, the World Health Organization (WHO) has turned to an experimental treatment: convalescent serum therapy. WHO approved its use as a treatment for Africans suffering with Ebola. The organization made this decision without comprehensive consideration of the historical precedent for provision of experimental therapy or scientific evidence for the safety and efficacy of plasma transfusion.

Variolation (cowpox inoculation) was first tested during the smallpox outbreak in Boston in 1721 by Cotton Mather, the famous New England cleric and physician.[3] That epidemic infected nearly half of the population (~12,000 citizens). The mortality rate for the outbreak was 14% for unvariolated individuals and 2% for variolated individuals. Mather's work prefigured the current process of clinical trials, in which scientists perform comparative analyses to determine efficacy. The hallmark of his procedure was controlled, randomized sample groups that featured subjects receiving treatment and subjects receiving the conventional care of the time. Today, drug testing is conducted in three phases.[4] Phase I tests 20-30 subjects to determine drug metabolism and toxicity. Phase II samples a relatively small group to examine effectiveness, short-term side-effects and risks. Phase III establishes effectiveness in a large population. A drug receives approval status only after passing rigorous standards set at each stage.

Problem Undertaking Phase II Trials in Africa

The current challenge in the Ebola epidemic is designing a proper Phase II trial in the African clinical environment. Current vaccine candidates, cAd3-EBOV (cAd3) from GlaxoSmithKline (GSK) and the U.S. National Institute of Allergy and Infectious Diseases (NIAID) and rVSVΔG-EBOV-GP (rVSV) from NewLink Genetics and the Public Health Agency of Canada, are not expected to complete Phase II trials until the first quarter of 2015.[5] Even then, they will most likely be available only to healthcare professionals volunteering for NGOs.[6] According to a recent article in the New England Journal of Medicine, "the design of these proposed trials in exposed populations raises many com-

plex questions that pit issues of scientific rigor against feasibility and acceptability."[7] There is no approved vaccine presently available for Ebola patients.

As with other clinical trials, a randomized, controlled trial generates the most robust data.[8] Subjects enrolled in studies must be asymptomatic but present evidence of early-stage disease progression. For example, patients infected with Ebola would need to be identified before the development of hemorrhagic fever and the diarrhea and vomiting that occur after a mean incubation period of 6.3 days.[9] This identification requires point-of-care detection technology that has not yet been utilized. Although there has been progress on the development of oral swabs for antibody detection and serum confirmation testing, these have not been subject to clinical scrutiny.[10]

Other factors that complicate clinical testing are traditional practices in West Africa that prompt family and friends to come in contact with sick individualws or hide loved ones because of a distrust of government officials.[1] For instance, due to years of armed conflict, Sierra Leone, Guinea and Liberia have a history of instability in their healthcare infrastructure.[11] For a Phase II trial, African patients exposed to Ebola would need to undergo plasma transfusions at the first sign of symptoms to test convalescent serum therapy for symptom reversal and recovery. This treatment could also be tested by prophylactically transfusing uninfected individuals to assess the overall infection rate. Either of these methods may prove to be a difficult undertaking given the current political situation.[12]

Testing for Efficacy

A study of the efficacy of convalescent serum therapy during the 2009 H1N1 influenza epidemic serves as a model for a comparative analysis in Ebola patients.[15] Subjects would be enrolled in a study with informed consent. Confirmation of infection would be established by reverse-transcription polymerase chain reaction (RT-PCR) detection of viral RNA.[10] Patients with contraindications for convalescent serum transfusion such as hypersensitivity to immunoglobulin would be excluded. Recovered patients would need to provide informed consent for donation of convalescent plasma. Whole blood would be drawn through an intravenous catheter and then centrifuged to collect plasma containing desired antibodies in a process called apheresis.[16] Plasma would then be screened for viral particles and Ebola-specific antibodies verified by RT-PCR to ensure adequate serum concentration. Results from convalescent serum transfusion in the H1N1 outbreak showed that treatment reduced mortality and viral load. Timely detection, informed consent, RT-PCR analysis and proper apheresis technique, though potentially effective, would be complicated procedures in resource-constrained Ebola Treatment Units (ETU).

WHO Proposal

A WHO meeting of medical ethicists in August 2014 concluded that the compassionate use of experimental therapies in regard to the Ebola outbreak is ethical.[17] Scientific research protocols demand a more nuanced approach. Rigorous protocols also arrive at a different conclusion with regard to the administration of unproven drug therapies. A decision by the United States Circuit Court of Appeals for the District of Colombia in Abigail Alliance for Better Access to Experimental Drugs vs. von Eschenbach summarizes the issues of access to Phase II experimental drugs. In the case of a terminally-ill Eb-

ola patient, once all approved treatment options such as hemodynamic monitoring and supportive care have been exhausted, there would be no further capacity to access experimental drugs. In the opinion of Abigail Aliance, a "broad right would harm terminally ill patients by endangering clinical research enrollment and the collection of reliable safety and effectiveness data".[18]

Convalescent serum therapy underwent a Phase I trial during the H1N1 outbreak. That trial established that plasma transfusions do not cause toxic reactions in patients. No complete Phase II trial on effectiveness of proposed Ebola treatments has been undertaken. Under the standards adopted by the scientific community, without evidence of effectiveness, the West African Ebola patient ought not be subjected to unproven therapies. The decision by the panel of medical ethicists convened by the WHO failed to meet this scientific standard.

Evidence of Efficacy of Convalescent Therapy

Evidence supporting the efficacy of convalescent therapy for Ebola is sparse. The scientific literature on efficacy has consistently determined that passive immunization of non-human primates that include the use of high-titer anti-EBOV equine immunoglobulin and the passive transfer of neutralizing human monoclonal antibody has resulted in no therapeutic utility.[19] A primate study published in 2009 extended these findings. It showed that transfusion of convalescent-phase blood from rhesus macaques to the Zaire Ebola Virus (ZEBOV) into 3 ZEBOV challenged monkeys resulted in no overall decrease in mortality.[20] Jahrling and colleagues urged caution in using convalescent serum therapy as a shortcut to a solution for Ebola and suggested further investment in more promising medications.

Most of the interest by WHO for convalescent serum therapy is based on a 1997 case study of patients in the Democratic Republic of Congo, which observed that there was a decrease in mortality after transfusions.[21] The authors, however, acknowledge that factors other than convalescent serum therapy that may have enhanced survival rates. Patients received supportive treatment that was markedly better than the that of normal patients during the 1997 epidemic. This complicates their findings on the effectiveness of convalescent serum therapy. It was concluded that survival after 5 days of Ebola symptoms and supportive care quality are predictors of overall mortality.[22]

An assessment of Ebola released by the WHO on September 26, 2014 outlined the apparent gaps in relevant clinical evidence. It also addressed concerns with the distribution of an interim guidance report for the National Health Authorities and Blood Transfusion Services.[23] In consideration of various treatment modalities, WHO observed that convalescent serum therapy "could be biologically plausible" and provided a detailed clinical guide. WHO deviated further from established scientific protocols in its approval of convalescent serum therapy when it noted that even if the therapy is non-effective the "byproducts of investment would be beneficial."[23] Among the potential benefits it included: "improvement of blood donation infrastructure and supportive care capacity."

Additional Concern with the WHO Approach

One of the concerns regarding the feasibility of plasma

transfusions is the possibility for transmission of secondary viruses such as HIV and Hepatitis A/C.[24] With the current disparity in blood screening protocols in the afflicted West African nations, increased plasma donations and transfusions may lead to greater rates of HIV infection. The amount of convalescent serum required for a large-scale transfusion would be prohibitive, given the current pool of Ebola survivors.[25] It is also doubtful that these countries have the capability of maintaining high standards for infection control to protect the healthcare workers who will need to conduct these donations. Lastly, these countries will not have widespread access to apheresis machines to filter blood donations. Consequently, they most likely will rely on primitive sifting and settling techniques. The remaining toxins, circulating immune complexes and soluble mediators of inflammatory that remain from sifting and settling may increase medical complications in recipients. Given a realistic assessment of current healthcare infrastructure in the effected areas of West Africa, the ability for convalescent serum therapy to provide a short-term solution seems improbable.

Conclusion

Amidst the hysteria associated with the current outbreak, healthcare professionals are being pressured to provide an answer—fast. The medical ethicists who agreed that providing experimental therapies as an effective means to satisfy these demands overlooked the importance of maintaining the standards of clinical research. The Director of the Center for Disease Control in Atlanta, in a recent podcast on the JAMA website, noted that decisions "are based on data."[26] In the United States, policy makers ultimately concluded that the public interest as well as the interest of terminally-ill patients is best protected by allowing access only to drugs of proven efficacy. Given the dearth of evidence for the efficacy of convalescent serum therapy, WHO ought not endorse this unproven therapy. WHO asserts that, should convalescent serum therapy not be effective, the secondary benefits of investment in the African healthcare infrastructure would be significantly constructive; this claim is wildly speculative. Desperately grasping for a solution to the Ebola crisis without credible evidence of the treatment's efficacy will not only fail the patients affected by Ebola in West Africa, but will delay the resolution of a lethal epidemic.

ENDNOTES

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