

COMMENTARY

Using convalescent whole blood or plasma as passive immune therapy for the global war against Ebola

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The number of Ebola infections from the current outbreak continues to grow with imported cases now being reported outside West Africa. There is an urgent need to develop immediate and effective countermeasures. Convalescent whole blood or plasma from patients who have recovered from Ebola virus diseases (EVD) is a unique resource that should be used on a larger scale through well-developed formal programs following the WHO interim guidance. This type of treatment has been proven effective in the past and it can contribute significantly to the control of the current Ebola outbreak.

The total number of Ebola cases from the current outbreak is reaching over 10 000 in 8 countries, including Spain and the United States, and this number may exceed 20 000 by early November 2014, based on estimates by the World Health Organization (WHO) Ebola Response Team.¹ The main strategy for combating Ebola remains community engagement to control outbreaks, including case management, surveillance, and contact tracing, a good laboratory service, safe burials, and social mobilization.² For those infected with Ebola virus, early supportive care with rehydration and symptomatic treatment improves survival. There is no effective treatment against the virus, and various immunological and drug therapies are under development. No licensed Ebola vaccines are available, but several potential candidates are undergoing evaluation with more human trials to be initiated.³

While such approaches are critical and useful for the prevention and treatment of Ebola, the high transmission potential of Ebola to

even well-trained healthcare workers and the high case fatality rate associated with Ebola infection (70.8%)¹ are significant barriers to achieving rapid control of the current outbreak. There is an urgent need to have practical and effective interventional approaches to reduce the impact of Ebola. At this point, frontline healthcare workers are working in a very high risk setting^{4,5} and they need to be armed with effective weapons to combat this deadly virus.

One unique resource that has not received enough attention is convalescent whole blood or plasma from patients who have recovered from EVD. Passive vaccination with high-titer immune sera or commercially-prepared polyclonal antibodies has been used successfully in the history of vaccination.^{6,7} In the 1930s, convalescent human sera were used for the treatment of measles and yellow fever.⁷ Convalescent human plasma was somewhat successful in treating patients of the great influenza pandemic of 1918.⁸ More recently, the use of convalescent plasma to treat patients with H1N1 flu has been reported to decrease mortality.⁹

Based on current WHO data, approximately 4000–5000 people throughout the world have survived Ebola infection. Their blood or plasma could be a very powerful weapon to provide highly effective treatment to people who are actively infected with Ebola.

It will take a considerable amount of time to prove that the vaccines and drugs currently under development are effective and for them to become widely available despite accelerated programs. The well-publicized trivalent monoclonal antibodies, Zmapp, that were used to treat two infected patients from the United States, were only useful when other compounding factors could not be fully excluded. Scientifically, appropriate immunological parameters and dominant antibody epitopes for correlates of protection are still

debated, as is the question of whether one or more antibodies are needed to form the polyvalent formulation for an effective vaccine or as therapeutic antibodies.

However, convalescent blood samples from Ebola survivors are readily available. Blood from those patients who survived with general supportive care only are of particular importance. The virulent nature of Ebola infection forces the body's immune system to mount a high-level protective antibody response to clear the virus, which can be confirmed through lab testing before a patient is released from medical monitoring or treatment. Natural viral infection is more capable of eliciting and maintaining high-level antibody responses compared to vaccination as shown previously.¹⁰

WHO recently issued a timely “*Interim Guidance for National Health Authorities and Blood Transfusion Services*” in September of 2014,¹¹ which provided a very detailed guidance on donor selection, screening, donation, and handling of blood and plasma units for the use of convalescent whole blood or plasma from patients who recovered from EVD. It also included guidance on the transfusion of convalescent whole blood or plasma to EVD patients, including informed consent collection and patient monitoring.

However, this document did not serve as a call for broader action to apply this well-established treatment strategy whenever possible. WHO and national health authorities in those countries affected by the outbreak should plan well-organized activities to expand this passive therapy program: (i) to establish a national central coordinating office to implement the above WHO interim guideline; (ii) to establish special criteria and process related to this program; (iii) collaboration with international experts in blood transfusion and passive immune therapy would allow for the establishment of a

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standardized blood collection and processing procedure that can be used in qualified medical and blood transfusion facilities; (iv) to stockpile and coordinate the use of collected and processed convalescent whole blood and plasma samples; (v) to train healthcare workers on the appropriate use of these treatments to clinically-indicated EVD patients and most significantly, to infected healthcare workers as they are important fighters in this war against Ebola; (vi) to recruit and educate EVD survivors for their participation in this program; (vii) to establish a database on the source, use, and outcome of such treatment; (viii) to save a small aliquot from each convalescent sample for subsequent in-depth immunological analysis, including Ebola-specific antibody titers and specificity of neutralizing antibody activities.

Such a national program can be established through financial and technical collaborations with international organizations and groups with greater technical expertise. Data learned from such programs will provide highly useful information for the development of vaccines and monoclonal antibody-based treatment.

A by-product of this program is the scientific feasibility of producing protective monoclonal antibodies from EVD survivors using peripheral blood mononucleated cells (PBMCs) from their donated blood. Rapid

progress in recent years in isolating single antigen-specific B cells from human PBMCs from which highly potent mAbs are produced¹² should allow for a similar process for the production of Ebola-specific mAb. However, this process is likely to take some time to develop and should not replace direct passive immune therapy with convalescent whole blood or plasma.

At least one case of passive transfusion with blood from an EVD survivor was reportedly administered to one of the nurses in the United States who was infected with Ebola through contact with her patient and the nurse subsequently recovered from the infection. However, a more organized program at international and national levels is critical to provide a much needed and effective weapon for healthcare workers fighting this war against Ebola. This is critical in breaking the chain of continued viral transmission to achieve ultimate control of the current Ebola outbreak.

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