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Review

Use of convalescent plasma in Ebola virus infection

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ABSTRACT

The recent Ebola virus epidemics which threatened three West African countries (Dec.2014—Apr.2016) has urged global collaborative health organizations and countries to set up measures to stop the infection and to treat patients, near half of them being at risk of death. Convalescent plasma—recovered from rescued West Africans—was considered a feasible therapeutic option. Efficacy was difficult to evaluate because of numerous unknowns (especially evolution of neutralizing antibodies), prior to the cessation of active transmission. This raises a large body of questions spanning epidemiological, virological, immunological but also ethical, sociological and anthropological aspects, alongside with public health concerns, in order to be better prepared to the next outbreak. This essay summarizes efforts made by a large number of groups worldwide, and attempts to address still unanswered questions on the benefit of specific versus non-specific plasma on altered—leaking—vascular endothelia in Ebola infection.

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Foreword (contextualization)

The last outbreak of Ebola Virus Disease (EVD) from December 2013 to April 2016 has called worldwide attention and called attention to both strengths and weaknesses of global preparedness plans against health threats in the XXI[st] Century. The first cases of this last epidemic were confirmed in March 2014, and the situation has been identified as a priority by the WHO during summer 2014. Three West-African countries were considered epidemic: Guinea, Liberia and Sierra Leone; 36 cases have been exported to other West African countries, Europe and North America; and it is now estimated that there have been more than 28,600 cases of clinical disease, with 11,300 deaths (meaning near 17,300 survivors) [1–4]. However, a non-negligible number of exposed, clinically non-infected individuals have been identified, though with large uncertainty. The EVD epidemic has been declared terminated by the WHO by the end of March 2016, with only erratic cases remaining [4].

During a year and half (summer 2015 to the end of year 2016), several consortia, under the auspices of the WHO and benefiting from special grants by diverse public and private funds, in Europe and North America developed strategies to combat the virus and its spread. In addition to epidemiologic means and containment measures, there were basically three intervention options: the development of antiviral drugs, the rapid development of vaccine strategies, and the design of immune therapies. Regarding this

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3rd option, there were several possible lines of action, i.e. principally the use of convalescent plasma (to be infused un-separated or fractionated into specific antibodies), or the engineering of neutralizing monoclonal antibodies [5]. Before these solutions could become available, the epidemic vanished and, for example, a large number of plasma units were recovered from convalescent individuals that have not been effectively transfused to newly infected persons. Thus, clinical trials reporting experiences are limited in size and some investigators acknowledge that conditions were not optimized to effectively obtain definitive data.

1. Introduction

Soon after the epidemic of EVD infection was recognized as a threat, public health authorities and the WHO made preparedness plans available; however, some scientific societies such as the World Apheresis Association (WAA) [6] along with other scientists [7,8] raised concerns about excessive delays in meetings the needs. WAA contributed an Open Letter to the Director of WHO to call attention to the potential benefit of plasmapheresis and transfusion of convalescent plasma, but also to the potential benefits of fresh plasma on leaking blood vessels [6]. Interest in the first part of the proposal has largely been shared with several consortia, while the second part gained attention with a more limited number of initiatives. The present State-of-the-Art paper, initially presented on the occasion of the 2016 Congress of WAA jointly with the XVIth Congress of the French Society, on April 27, in Paris, aims at briefly to report the use of convalescent plasma therapy in EVD infection and to introduce some information on the benefits of fresh, non-specific, plasma as well.

2. Convalescent plasma and plasma therapy

Convalescent plasma refers to a plasma therapy based on plasma or plasma derivatives obtained from donors having recovered from [in general] severe infection and infused into newly infected individuals. This type of therapeutic intervention is not novel, as it has been used regularly over a centenary to deal with most life threatening epidemics (reviewed in [9]), until other therapeutic means were made available; however, it may still be an operative therapy, as interest has not vanished in more than 100 years (the first well documented occurrence being the Spanish Flu in 1917–1919) [10]. Many reports deal with periods where antiviral drugs were virtually absent, and several recent experiences have tested the effects of convalescent plasma on SARS, MERS, 2005 A/H5N1 flu, 2009 A/H1N1 flu, Chikungunya, etc. [11–13].

3. Questions raised by plasma therapy and convalescent plasma

As a large experience has accumulated, questions raised to obtain, process and use convalescent plasma are now listed:

- How to access blood donors?
- Preference of plasma obtained in large volume by repeated apheresis over smaller volumes of recovered plasma from whole blood?
- How to guarantee ethical principles?
- How not to avoid altering donors' health, especially if formerly sick?
- How to solve technical problems in unfavorable environments (power supply, shipping logistics, quarantine and containment, viral biohazards, etc.)?
- The value of extending testing for other infectious pathogens that can be sampled with blood or plasma, in endemic countries? And to what extent?
- The value of inactivating pathogens in plasma from apheresis or whole blood, regarding the risk of [other] infectious pathogen transmission?
- How best to identify or select patients to benefit from this therapy: intent to care or compassionate?
- How to insure that convalescent plasma contains sufficient neutralizing antibodies (NAbs)? How to define NAb development: what is the development course, and in particular are there still persistent viruses by the time where Abs can be detected? How long after clinical resolution of symptoms is there a chance to obtain NAbs if any? Are all Abs neutralizing or are there also cross-reactive, potentially facilitating Abs? (as recently seen between Dengue and Zika viruses [14])?
- How understanding the issue of concurrent infections and subsequent inflammation, as has been recently emphasized with the suspected benefit conferred by malaria infection [15]?
- How to monitor each step to make sure that so-called convalescent donors were indeed infected and that newly infected patients are viraemic?
- How to ensure global safety and quality at each step of the process?
- Etc.

4. Principles of plasma therapy for severe viral infections

There are two assumptions: One major, and one minor. The major assumption is that convalescent plasma contains protective Abs, ascribed as NAbs, that are transferable from a symptom-free donor—having however recovered from proven or documented infection—to a newly infected patient. The use of plasma from non-human hosts is prohibited for the time being, for immunological but also cross-species infection safety reasons, but the question is still open regarding purified and virus-inactivated Ab preparations. The minor assumption is that plasma can convey other healing factors that may be therapeutic in hemorrhagic fevers even in the absence of NAbs. While the major assumption is not debated at all because it represents the essence of plasma therapy, the second one is theoretical and it postulates that plasma—and neither serum nor purified Igs—is the preferential support therapy; it addresses the issue of leaking vessels (hemorrhagic fevers) only, as fresh plasma also contains factors that restore the endothelium glycocalyx [16]. It is interesting to consider that few consortia have considered this point, however, despite an interesting lesson that could have been learnt from the Lassa infection episodes which demonstrated benefit from plasma therapy in the 80's [17], but received—in our opinion—too little attention. A very recent report from the French Army Transfusion Service (CTSA) supports this hypothesis [18].

5. Plasma therapy and EVD infections: from the proof of concept to the initiation of therapy

The proof of concept for convalescent plasma therapy dates back to 2001 where Gupta et al. demonstrated the neutralizing effect of mouse Abs in an experimental model [19].

Before consortia handled the collection and the transfer of Plasma or Abs, initial recommendations were issued by some of us (scientists/specialists), prior or concomitantly to the release of the WHO guidance for plasma collection (2014) [20], and the WHO interim guidance for Ethics review [21]. The "Ebola_Tx Consortium" contributed a couple of publications on its organization and on the trial concept, along with other similar initiatives [22–29]. The "Ebola_Tx Consortium" released its first report in the *New Eng J*