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Transfusion and Apheresis Science 51 (2014) 120–125

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Review

Ebola virus convalescent blood products: Where we are now and where we may need to go

Thierry Burnouf [a,*], Jerard Seghatchian [b,**]

[a] Graduate Institute of Biomedical Materials and Tissue Engineering, College of Oral Medicine, Taipei Medical University, Taipei, Taiwan
[b] International Consultancy in Blood Components Quality/Safety Improvements, Audit/Inspection and DDR Strategy, London, UK

ARTICLE INFO

Keywords:
Ebola
Blood
Plasma
Convalescent plasma
Transfusion
Immunoglobulins
Mini-pool
Viral inactivation
Emerging pathogens
Virus

ABSTRACT

The world is regularly exposed to emerging infections with the potential to burst into a pandemic. One possible way to treat patients, when no other treatment is yet developed, is passive immunization performed by transfusing blood, plasma or plasma immunoglobulin fractions obtained from convalescent donors who have recovered from the disease and have developed protective antibodies. The most recent on-going epidemic is caused by the Ebola virus, a filovirus responsible for Ebola virus disease, a severe, often lethal, hemorrhagic fever. Recently, the use of convalescent blood products was proposed by the WHO as one early option for treating patients with Ebola virus disease. This publication provides an overview of the various convalescent blood products and technological options that could theoretically be considered when there is a need to rely on this therapeutic approach. In countries without access to advanced blood-processing technologies, the choice may initially be restricted to convalescent whole blood or plasma. In technologically advanced countries, additional options for convalescent blood products are available, including virally inactivated plasma and fractionated immunoglobulins. The preparation of mini-pool immunoglobulins is also a realistic option to consider.

Contents

* Corresponding author. Graduate Institute of Biomedical Materials and Tissue Engineering, College of Oral Medicine, Taipei Medical University, Taipei, Taiwan.
E-mail address: thburnouf@gmail.com (T. Burnouf).
** Corresponding author. International Consultancy in Blood Components Quality/Safety Improvements, Audit/Inspection and DDR Strategy, London, UK.
E-mail address: jseghatchian@btopenworld.com (J. Seghatchian).

http://dx.doi.org/10.1016/j.transci.2014.10.003
1473-0502/

1. Introduction

Recent infectious agents include the West Nile virus (WNV), Dengue virus, chikungunya virus, severe acute respiratory syndrome (SARS) virus, Middle-East coronavirus, various avian flu viruses (H1N1, H5N1) some with a pandemic potential, and Ebola virus (EBOV) [1–3]. Transfusion of convalescent blood products may be considered for treating patients affected by emerging infectious agents when no other specific treatment is yet available and if the infection generates effective protective antibodies. Transfusing convalescent blood products has demonstrated some efficacy in fighting various viral or bacterial infectious diseases including influenza, measles, chickenpox, and, more recently, SARS and the HIN1 and H5N1 avian flu viruses [4–9]. Convalescent blood products are obtained by collecting blood (or plasma) from a donor, that preferably lives in the same geographically infected area, to account for potential mutations of the virus, and who has survived a previous infection by developing antibodies. Convalescent blood products are transfused to achieve passive immunization in recipients by neutralizing the pathogen, eventually leading to its eradication from the blood circulation.

EBOV, a member of the family Filoviridae, is the most recent example of an infectious outbreak that is now affecting West African countries. In the absence of a licensed therapeutic product yet, such as a vaccine or an antiviral treatment, the World Health Organization (WHO) recently approved in principle the evaluation, under certain conditions where controlled clinical studies would evaluate safety and efficacy [10] and in the absence of current alternatives, the use of convalescent "serum" as the first therapeutic option to treat patients with EBOV [10–12]. Part of this decision relied on historical data on the use of convalescent blood products against various infections and on a 1999 report which found that an infusion of convalescent whole blood was associated with the survival of seven of eight Ebola patients in the Democratic Republic of Congo [13]. In 1977, a (heat-treated) convalescent Ebola "serum" was infused, together with human interferon, into a research investigator who had accidentally been infected by EBOV [14]. Animal studies suggested the potential protective effect of anti-EBOV antibodies [15]. Individuals who have survived a previous infectious outbreak are possible donors of convalescent blood that potentially contains protective and long-lasting immunoglobulins (Igs). Serological cross-reactivity between various EBOV strains was found [16], which may potentially increase the number of potential donors to treat people affected with the recent outbreak. At this stage, the efficacy and safety of transfusing Ebola convalescent blood products have not been fully proven although it is suspected that it may help for the treatment. It was suggested that antibody-dependent enhancement (ADE) of filovirus infections may be a risk [17,18], but the clinical relevance of ADE is controversial [19]. In this document, we attempt to clarify the types of convalescent blood products that can be considered to treat patients with EBOV and, more generally, other viral infections.

2. Historical perspectives

The use of animal-derived serum or human convalescent blood products was first reported in the early 20th century to treat various infections when vaccines or other treatments such as antibiotics were not yet available. Many reports lack important technical information on product preparation procedures, and the terms used may be misleading (e.g., the term "serum" may be employed in a generic way to designate other blood products). Use of convalescent "whole blood", or serum obtained by letting the blood clot, was reported against influenza [20] (see Refs. 8 and 21), mumps [9], Herpes zoster [22], poliomyelitis [23], typhoid fever [24], and measles [7,25]. In some of those early clinical examples, whole blood was converted into serum by allowing it to clot, as described for treating measles patients, and injected by an intramuscular route [7]. Alternatively, serum was obtained by adding calcium chloride, and then pooling and sterile-filtering it [25]. A citrate anticoagulant may be added to blood, and then the plasma is recovered by decantation [7], not centrifugation. Use of convalescent "defibrinated plasma" was described in cases of chickenpox [26].

3. Current options

Modern blood transfusion allows the preparation of a range of products that are known to have controlled safety when prepared following standardized, monitored procedures. It should be kept in mind that even in those countries with advanced blood-collection organizations, collecting convalescent blood products during an epidemic crisis creates substantial organizational difficulties [27] and therefore requires adequate preparation [6]. Collection of convalescent blood/plasma in low-income economies, which are most susceptible to being affected by devastating epidemics, can face major organizational, technological, and human challenges, including controlling convalescent donors' being clinically and virally free of infections, pathogen testing (e.g. Human Immunodeficiency virus, hepatitis B virus, hepatitis C virus, malaria agent, and syphilis) temperature control of the production chain, processing, and traceability.

Figure 1 summarizes technical options that should be considered when preparing convalescent blood products.

3.1. Whole blood

As reported in 1999, convalescent whole blood was used in the Democratic Republic of Congo to treat eight Ebola patients, seven of whom survived [13], although this high rate of survival could not be necessarily ascertained to be related to the blood transfusions. To be optimally effective in controlling hemorrhagic events, as may occur with EBOV disease, whole blood collected with an anticoagulant solution should be transfused within 24 h to maintain viable platelets and clotting factors (which implies that the viral testing and ABO and RhD cross-matching immunohematological and compatibility tests should be performed within that period if donors have not been pre-screened prior to donation). Whole blood can also be stored at 2–6°C for several days (e.g. 35

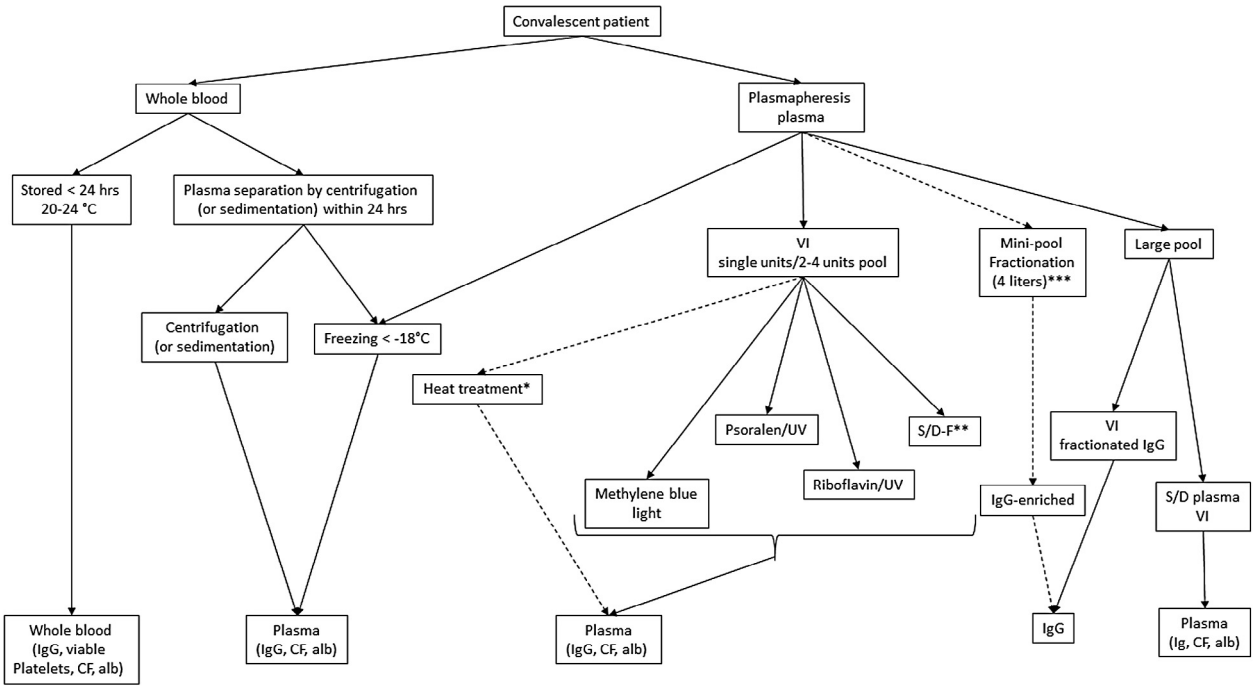

Fig. 1. Flow-chart presenting the various technical possibilities that currently can theoretically be considered for producing convalescent blood products. Virally-inactivated plasma and immunoglobulins can also be made from recovered plasma. *unlicensed; **developed in Egypt; ***under clinical trial in immuno-deficient patients; IgG: immunoglobulin G; CF: coagulation factors; alb: albumin; S/D: solvent/detergent; S/D-F: solvent/detergent-filtered; UV: ultraviolet light; VI: virally-inactivated.

days if collected in citrate phosphate dextrose with added adenine).

3.2. Plasma

In the last few years, convalescent plasma has been the blood fraction successfully selected for transfusion to patients affected by Argentine hemorrhagic fever (Junin virus) [28], SARS [29–32], H1N1 [33], and H5N1 [5,34]. There is also a report on the administration of Lassa fever convalescent plasma (LFCP) to 27 hospitalized patients in Nigeria, with apparently increased efficacy in the outcome of the disease when plasma was infused early enough after the diagnosis [35]. Plasma can be obtained by centrifugation, or decantation, of whole blood or by apheresis. Apheresis is the preferred mode of collection for several reasons: larger volume collected/session, possibility of more frequent donations, and absence of impact on the hemoglobin level due to the reinfusion of the red blood cells.

4. Virally reduced (inactivated) single/small pooled plasma

4.1. Technologies licensed in Europe and other countries

Single plasma units: Several viral inactivation technologies of plasma for transfusion applicable to single units have been developed, validated, and licensed in several countries. In principle, use of a viral-inactivation process on convalescent plasma is preferable, if technically achievable, in case there are uncertainties with the possibility of residual viruses in the plasma. It, however, should not be a substitute to good donor screening and optimal viral testing. Licensed technologies include treatment with methylene blue/light [36], psoralen (S-59)/ultraviolet (UV) [37], and riboflavin/UV [38]. Readers can find detailed reviews addressing the technical characteristics, advantages, and limits of these technologies as applied to plasma for transfusions [1,39–41]. All of them use a viral-inactivation process of photoinactivation in the presence of a photosensitizer. They require a dedicated bag treatment system and a specific proprietary illumination machine. Operators should receive appropriate training as needed for all such procedures. To our knowledge, there are no published data relative to the inactivation of EBOV using these technologies. Although these methods tend to induce some loss in the activity of coagulation factors, including factor VIII and fibrinogen, they are thought not to affect immunoglobulin functional activity.

4.2. Technology approved in Egypt

Solvent/detergent (S/D)-filtered (S/D-F) plasma: This technology is routinely used in one blood center in Egypt; 400–450 mL of plasma for transfusion is virally inactivated in a single-use, CE-marked bag system by S/D using 1% tri (n-butyl) phosphate/1% Triton X-45. The S/D agents are eliminated by oil extraction and filtration, and plasma is sterile-filtered before online dispensing in a storage bag and freezing [42]. The method was validated to ensure the inactivation of >4 log of several enveloped viruses, including HIV, within a few minutes of treatment. It is thought

that just like HIV, HBV and HCV, EBOV, being an enveloped viruses, should be readily inactivated by S/D treatment.

4.3. Experimental, unlicensed technologies

A 3-h-long 50 °C liquid heat-treatment of plasma in its collection bag and in the presence of stabilizers compatible with transfusion was described [43]. The process was validated to inactivate >6.6 log of human immunodeficiency virus (HIV), and >4 log of hepatitis A (HAV) and C (HAC) model viruses. The procedure was used to prepare convalescent scrub typhus plasma and test its HIV-inhibitory action in 10 HIV-1-infected patients [44] following earlier studies which found the presence of plasma-borne HIV-1-suppressive factors produced during some scrub-typhus infections [45]. This system is not commercially available and could not be implemented in a short term.

Another experimental plasma heat-treatment at 56 °C for 30 min was used for randomized clinical evaluations assessing the potential benefit of passive immunotherapy of HIV-1 seropositive plasma. Serial transfusions were made on 18 AIDS patients in the first study [46]. In a second randomized controlled trial, 86 HIV-1 patients received a 300-mL infusion of heat-treated plasma every 14 days over a 1-year period, and every 28 days thereafter [47]. Care should be taken, as with any heat-treatment procedure, to minimize alterations (e.g., aggregation) of proteins that could lead to possible adverse events in patients.

An experimental process allowing viral removal of plasma for transfusion by filtration on 75–35 nm hollow fibers was described [48]. It can remove viruses larger than 35 nm without substantially affecting the IgG content. The size of EBOV (approximately 120 nm) should in principle ensure its removal. No commercial device for this application to plasma has been made available yet.

5. Mini-pool Immunoglobulins

A mini-pool plasma fractionation process using disposable licensed or CE-marked production devices and based on caprylic acid precipitation to purify and virally inactivate immunoglobulins is under development in Egypt [49]. The current process scale is 4 L allowing the pooling of approximately 20 plasma donations. The treatment was validated to inactivate lipid-enveloped viruses, confirming other observations [50,51]. This immunoglobulin product is currently under clinical evaluation in Egypt [52]. Such minipool processing approach, which needs only a small production area equipped with laminar flow cabinet, may be particularly suited for preparing IgG from mini-pools of convalescent plasma within reasonable delay and minimal infrastructure requirements.

6. Large-pool products

Two types of large-scale product can theoretically be considered to produce convalescent blood products.

Industrial S/D plasma is a pooled plasma for transfusion that is virally inactivated by S/D treatment and requires a pharmaceutical-grade facility for its preparation. Considering its proven robustness against a wide range of enveloped viruses [53], this S/D process should also inactivate the EBOV [54], should the virus be present in convalescent plasma. The pool size for industrial S/D plasma generally ranges 100–2500 donors, depending upon the manufacturer and local regulations addressing risks from infectious agents (e.g., non-enveloped plasma-borne viruses) not inactivated by S/D treatment. To our knowledge, there has been no example of preparation of industrial S/D-treated convalescent plasma.

Large-scale fractionated intravenous Igs: Normal intravenous Igs (IVIGs) are prepared by fractionating large pools (typically 2000–4000 L) of human plasma collected from approximately 10,000–40,000 donors [55,56]. This pool size is obviously too large to be considered due to the difficulties to generate enough convalescent plasma. In some facilities, hyperimmune Igs are made from smaller pools (100–1000 L) of plasma from donors identified to have high titers of specific antibodies. Licensed hyperimmune IgG includes anti-HBV, anti-tetanus, anti-rabies, anti-cytomegalovirus, and anti-rhesus immunoglobulins. They are now typically made from donors who were immunized through routine vaccinations with licensed vaccines or controlled immunization protocols [57]. Hyperimmune IgG can also be experimentally produced from the plasma of donors immunized by natural infectious routes, as described for instance for malaria [58]. Commercial IgGs are made in good manufacturing practice-inspected facilities following licensed production methods. They are subject to at least two distinct viral-reduction steps [56]. IgGs made from convalescent plasma were experimentally prepared on a small scale to treat patients with SARS [30,59]. Normal IVIG preparations made by the plasma fractionation industry may contain substantial levels of antibodies against infectious agents when collected from donors who happened to have been seroconverted during previous infectious outbreaks. Some commercial IVIG products may have high antibody titers against WNV [60,61], HAV [62], measles [63], or Dengue virus when made from plasma collected from populations including donors who were naturally infected or vaccinated. Preparation of convalescent IgGs in a licensed facility would create specific, probably unsolvable, GMP (good manufacturing practices) issues considering the strict regulatory requirements to which plasma fractionators should adhere, particularly regarding the quality and safety of plasma for fractionation [57].

The production of any large-pool products, either industrial S/D plasma or IVIG in countries with advanced national regulatory authorities, should – under standard guidelines applying to licensed products – use plasma that meets strict quality specifications (epidemiological surveillance, donor screening, viral testing, blood/plasma processing, storage, transportation, traceability, etc.) [57] which convalescent plasma from low- or medium-income countries is unlikely to meet in the foreseeable future. Therefore, the manufacture of large-pool anti-EBOV IgG and S/D-treated industrial plasma seems to be very challenging.

7. Conclusions

Considering the seriousness and the high mortality rate of the infection, it is important that patients affected by EBOV

be urgently given a chance to receive safe convalescent blood products that can potentially save their life. Several products and diverse technologies can be considered for preparing convalescent blood or blood-derived therapies to fight EBOV and other emerging infectious agents. Whole blood and plasma may be the first and only options to consider before other approaches, provided they are prepared under ethical and controlled conditions. Production of safe convalescent blood products should rely, whenever possible, on a well-structured and well-coordinated national blood-collection organization which is not the case in currently affected countries in West-Africa [64]. This structure can serve as a technology platform when convalescent blood is collected – for safety considerations and to guarantee the traceability or because there is no other choice – under a distinct setting (e.g. remote health care centers). The efficacy and modality of clinical use of convalescent blood products should not be taken for granted. Controlled clinical evaluations are also, therefore, important to establish safe modality of treatment and to provide important knowledge for the treatment of future infectious outbreaks. Convalescent blood products should be prepared and used under strict controls and monitoring to ensure optimal safety to both donors and recipients. A recently published WHO Guidance document provides further technical information on the preparation of convalescent blood products [65].

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