

WHO Blood Regulators Network (BRN)

Position Paper on Collection and Use of Convalescent Plasma or Serum as an Element in Pandemic Influenza Planning*

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1 Consideration of the use of convalescent plasma as an element in pandemic preparedness and planning

1.1 Overview

Addressing the threat of pandemic influenza from recently emerged influenza viruses has become an urgent global public health priority.

Current pandemic planning includes stockpiling of antiviral drugs, development of candidate vaccines and planning for production of vaccines against the actual pandemic strain when it is identified. However, there are currently no scientific assurances that these strategies will be guaranteed to provide protection due to factors such as limitations or delays in vaccine availability and the potential for development of resistance to antivirals. Moreover, despite effective drugs and vaccines, there is a high likelihood in a pandemic that large populations of susceptible persons will become ill especially early in a pandemic. Therefore, it is prudent to explore other options to be included in pandemic preparedness including the production and use of convalescent plasma or serum as a useful addition to other pandemic planning measures. Based on animal models of influenza pneumonia, the possibility exists that passive immunotherapy with convalescent plasma or serum might be effective as a therapy to reduce disease severity. This concept is supported by a case report of a viral response to convalescent plasma in a patient with H5N1 pneumonia (NEJM 357:14, 2007). Additionally, the only recent meta-analysis that refers back to the use of convalescent serum in the 1918 flu pandemic, has suggested that early administration of convalescent serum was effective in reducing mortality (Ann Int Med 2006; 145:599-609). These reports raise the question whether strategies for collection and therapeutic use of convalescent plasma or serum should play a role in preparedness for pandemic influenza. Validation of such a strategy remains to be explored. Development of fractionated immunoglobulins or monoclonal antibodies also might be considered.

1.2 Background

Serum therapies were successfully used to treat many infectious diseases (anthrax, plague, scarlet fever, measles, tularemia, diphtheria, dysentery, meningococcal meningitis, rabies, pneumococcal pneumonia) for half a century after Emil von Behring first demonstrated their effective use as a therapeutic in diphtheria. Their general use fell into disfavor after the advent of antibiotic therapies and in consideration of the problems of adverse reactions to animal derived sera and whole serum. However, human and animal derived immune globulins remain important therapies for a variety of conditions (parvovirus, CMV, hepatitis B, rabies, hepatitis A, botulism, envenoming, etc.). Additionally, there is precedent in the modern era for effective management of Argentine Hemorrhagic Fever (Junin Virus) with immune plasma as part of a nationally organized

response (Lancet 314(8154): 1216-1217, 1979). By analogy, although there are many uncertainties, the possibility exists that convalescent plasma might play a role in the urgent response to pandemic influenza in settings where vaccination and/or effective antiviral chemotherapy is lacking.

2 Position Statement of the WHO Blood Regulators Network (BRN) on the Collection and use of Convalescent Plasma or Serum

2.1 Role of Regulatory Agencies

Although convalescent plasma or serum could be prepared and used locally as a medical practice, an organized effort to establish safe use and to determine true efficacy of this therapy has to be established by applicants and well controlled by regulatory authorities. Such an approach is needed especially in consideration of the likelihood that convalescent plasma or serum will be used empirically without defined standards in urgent conditions of a flu pandemic when effective vaccine, antiviral drugs and antimicrobial agents are unavailable or prove to be inadequate. In conjunction with public health agencies, regulatory authorities could play a role in identifying the need for a scientific evaluation in this area. Countries which want to engage in this type of practice should bring together industry and/or blood establishments to design and set up a program for collection of convalescent plasma or serum and to determine the feasibility for its use. Feasibility should include as well, the capacity for production at a large scale. Moreover, design of clinical trials for proof of concept should be regulated by national authorities. For example, it is suggested that efforts could be directed to carrying out trials using convalescent plasma, serum or immunoglobulin prepared from individuals who have convalesced from seasonal flu as a model for feasibility and to study effectiveness in seasonal flu cases where vaccination was not performed or was not effective.

2.2 General Regulatory Considerations

A regulatory approach rather than solely a medical practice approach to empirical use of convalescent plasma or serum in pandemic influenza would have advantages in promoting patient safeguards and the collection of useful scientific information. The following issues warrant consideration by blood regulatory authorities:

- **Clinical use of convalescent plasma or serum should be regarded as investigational**

Because the safety and efficacy of convalescent plasma or serum are unproven, clinical use of this product should be managed as an experimental therapy consistent with ethical safeguards (informed consent, institutional approval, special labeling) and a commitment to gather and report outcome data.

- Standards for product manufacturing should maximize safety of donors and recipients

Collections should be performed by trained staff operating under standard operating procedures in regulated and certified facilities that are routinely engaged in blood and plasma collection. Selection criteria for donors should include all established safeguards for prevention of transfusion transmitted diseases (see “WHO Blood Regulators Network (BRN): Donor selection in case of pandemic situations” at <http://www.who.int/bloodproducts/brn/DonorSelectionincaseofPandemicSituations.pdf>).

Additionally, standards should be established for diagnosis of recent influenza in the donor (e.g. a case definition and/or antibody titer), time post resolution of illness, and number of standardized collections per donor. Where feasible, pathogen inactivation of plasma is desirable. Care should be taken to minimize disruption to the collection and processing of blood and components for other patient needs.

- Criteria for patients to be treated

Development of a case definition for confirmation of disease in a candidate patient might prevent delay of therapy in settings where specific diagnostic testing is impractical. Also, it may be useful to establish priorities for clinical use (e.g. use early in onset of influenza pneumonia vs. use reserved for advanced disease).

- General considerations for plasma products are applicable

As with other plasma therapies, attention should be given to ABO compatibility. As feasible, preference for male sourced plasma or serum (and/or testing of female donors for antibodies to HLA and anti-granulocyte antibodies) may minimize risk of TRALI. Dosing guidelines should be provided and consideration should be given to use of units from at least two different donors in recognition of biologic variations in the immune response.

- Outcome monitoring should be oriented towards determination of product efficacy and the rapid communication of best practices

Patient outcome monitoring and reporting should include indicators of safety and efficacy. Additionally, specimen collection from both donors and recipients should be performed to permit retrospective determination of the characteristics of an effective product and dosage regimen. Mechanisms for rapid aggregation of clinical experience and dissemination of information to clinicians should be established in advance of a pandemic.

3 Summary

The WHO Blood Regulators Network recommends that scientific studies on the feasibility and medical effectiveness for collection and use of convalescent plasma or serum, and possibly fractionated immunoglobulins, be explored through clinical trials. In particular, an opportunity exists to study the feasibility and effectiveness of convalescent plasma or serum and possibly other passive immunotherapies in severe seasonal influenza as well as in pandemic situations. Acting within their mandates, regulatory agencies can play an essential role to enable progress in this area. Countries which want to engage in this

type of practice should take all necessary steps to establish appropriate regulatory conditions for the collection of convalescent plasma or serum and the conduct of clinical studies. Programs conducted at the national level should ensure the use only of convalescent plasma or serum collections that meet the safety, quality and efficacy criteria consistent with established regulatory standards. The feasibility of production on a large scale should be considered based on the outcome of studies.
