Development of plasma therapies for emerging infectious diseases

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Therapeutic Goods Administration (TGA)

- A part of the Australian Government Department of Health
- Main offices in Canberra – satellite offices in Sydney, Melbourne, Adelaide and Brisbane
- Regulates the safety, quality and efficacy of therapeutic goods in Australia
- Regulates medicines, devices, biologicals and blood
- Operations are primarily cost recovered (98%) industry pays fees for making applications and annual charges for products they are responsible for
Overview

• Background
• History of plasma therapies for infectious diseases
• Products currently in use
• Convalescent plasma – drivers/issues
  - considerations for use
• Initiatives to support potential use
Background

Plasma therapies for infectious diseases

• Based on the concept of passive immunization (PI)

• PI is a technique to achieve short term immunisation against infectious disease agents by administrating pathogen specific antibodies

• whole blood, plasma, serum or immune globulin concentrates

• consider the use of convalescent plasma or serum as a potential addition to other measures of preparedness for and response to infectious disease epidemics
History

Past use

• In 1890 Emil von Behring first demonstrated antibodies effective as a therapeutic for diphtheria. Nobel prize 1901.
• Supported growth of pharma industry.
• Successfully used to treat many infectious diseases including anthrax, plague, scarlet fever, measles, tularemia, diphtheria, dysentery, meningococcal meningitis, rabies, pneumococcal pneumonia
• Use declined significantly after the advent of antibiotics.

West German postage stamp (1954) commemorating Paul Ehrlich and Emil von Behring
Current use

• Human and animal derived immunoglobulin concentrates remain important therapies for a variety of viral and bacterial infectious diseases.

• European monographs for human immunoglobulin against:
  - viruses: Hepatitis A, Hepatitis B, measles, rabies, rubella, varicella and normal (hepatitis A, measles, poliomyelitis or rubella)

• European monographs for animal immunoglobulin against:
  - bacterial toxins – botulinum, diphtheria, gangrene, tetanus
Current use

• In Australia the following human immunoglobulins are supplied under the national supply arrangements (reimbursed): CMV, Hepatitis B, Zoster and normal (to treat susceptible contacts of an indicated infectious disease (hepatitis A, measles, poliomyelitis or rubella))

• Other human immunoglobulins approved for supply in Australia but NOT under national supply arrangements include rabies and tetanus immunoglobulin
Future use – convalescent plasma

Definition

- plasma obtained from a person who has recovered from an infectious disease and considered to be especially rich in antibodies against the infectious agent of the disease

https://www.merriam-webster.com/dictionary/convalescent%20serum
Future use – convalescent plasma

Some drivers for use

• Rapidly emerging virus epidemic associated with high morbidity or mortality
• Especially early in the event, prior to availability of effective vaccines and antiviral therapies
• Based on the concept of passive immunization
• Supported by historical experience

• Part of epidemic preparedness
Future use – convalescent plasma

Evidence base

• Precedent in the modern era for effective management of Argentine Hemorrhagic Fever (Junin Virus) with convalescent immune plasma as part of a nationally organized response\(^1\).
• More recently other agents have also been targeted including Ebola\(^2,3\).
• Other trials but low level evidence (small numbers, no control arm)

Future use – convalescent plasma

Issues

• Potential efficacy dependent generation of neutralizing antibodies or otherwise mediate an effective immune response
• Effective therapeutic dose
• Use of serum, plasma or immunoglobulin concentrate
• Preparation of an immunoglobulin concentrate, higher potency and greater consistency (multiple donors)
• Availability and feasibility of assays useful to select donations likely to be therapeutic, e.g. based on high titer of a total or neutralizing antibody
Future use – convalescent plasma

Issues

- Potential harm including risk of unintended transmission of undetected infectious agents present in the donor or immune enhancement due to transferred antibodies exacerbating the disease (eg dengue, use anti-viral immune responses to infect host target cells)
- Using pathogen inactivation and reduction technologies
- In country capability (ethical, scientific, and logistic resource issues)
- Close cooperation with mature regulatory authorities experienced in this field and WHO
- Aim for a timely and controlled approach ensuring safety, as well as documentation and scientific evaluation of outcomes

In country capability
Future use – convalescent plasma

Considerations (from draft WHO BRN position paper)

- **Clinical use of convalescent plasma or serum should be regarded as investigational.** As an experimental therapy should be ethical safeguards (informed consent of donors and patients, institutional approval, special labeling) and a commitment to gather and report outcome data independently of the outcome of the study.
Future use – convalescent plasma

Considerations

- **Standards for product manufacturing should maximize safety of donors and recipients.**
  - Collection and manufacture by trained staff operating under standard operating procedures in accordance with international guidelines
    
  - Assays ideally using nucleic acid amplification technology (NAT) to demonstrate resolution of the infection, titer of (neutralizing) antibodies.
  - Use donations that are negative for HBV, HCV, HIV, syphilis or other locally transmitted infections.
  - Pathogen inactivation of plasma is highly desirable.

Future use – convalescent plasma

Considerations

- **Criteria for patients to be treated.** Case definition for confirmation of disease in a candidate patient. Dosing guidelines (units from at least two different donors). Establish priorities for clinical use (early or advance phase disease).

- **General considerations for plasma products are applicable.** ABO compatibility if plasma used.

- **Outcome monitoring should be oriented towards determination of product safety and efficacy and the rapid communication of best practices.** Specimen collection from both donors and recipients (pre- and post-treatment) for retrospective determination of the characteristics of an effective product, dosage regimen and patients having most benefit. Rapid aggregation of clinical experience and dissemination of information.
Future use – convalescent plasma

Considerations

• **Potential use of small scale immunoglobulin concentrates** Technology exists to prepare virally inactivated immunoglobulin concentrates from small pools of plasma units\(^1\).

• **Feasibility of large scale production including manufacture of purified immunoglobulins** Limited by lack of sufficient donations during early phase of epidemic, for recurrent epidemic consideration of identifying donors and stockpiling product. Issues around export import.

1. El-Ekiaby M, Vargas M, Sayed M, Gorgy G, Goubran H, Radosevic M, Burnouf T. Minipool Caprylic Acid Fractionation of Plasma Using Disposable Equipment: A Practical Method to Enhance Immunoglobulin Supply in Developing Countries. [http://dx.doi.org/10.1371/journal.pntd.0003501](http://dx.doi.org/10.1371/journal.pntd.0003501)
Future use – convalescent plasma

Summary points for use of convalescent plasma

- Consider candidate intervention in the setting of an expanding viral epidemic of public health concern for which vaccines and antiviral drugs are unavailable.
- Development of the infrastructure to permit safe collection and use of convalescent plasma or serum should be part of national epidemic preparedness.
- Feasibility and medical effectiveness for collection and use of convalescent plasma or serum should be explored through clinical trials.
- Convalescent plasma or serum collections should meet the safety and quality criteria consistent with established regulatory standards.
- Concentrates of immunoglobulins may provide products of higher potency and greater consistency than individual units.
Future use – convalescent plasma

Initiatives

• European Commission and European Medicines Agency funding
• WHO guidelines
  – Use of convalescent whole blood or plasma collected from patients recovered from Ebola virus disease
  – Ethics of using convalescent whole blood and convalescent plasma during the Ebola epidemic

• WHO Blood Regulators Network position papers
  http://www.who.int/bloodproducts/brn/en/
Questions