Use of convalescent plasma in COVID-19

Stockholm, 31 March 2020

Management of patients with COVID-19

Hospital management of pneumonia and ARDS

Vaccine candidates

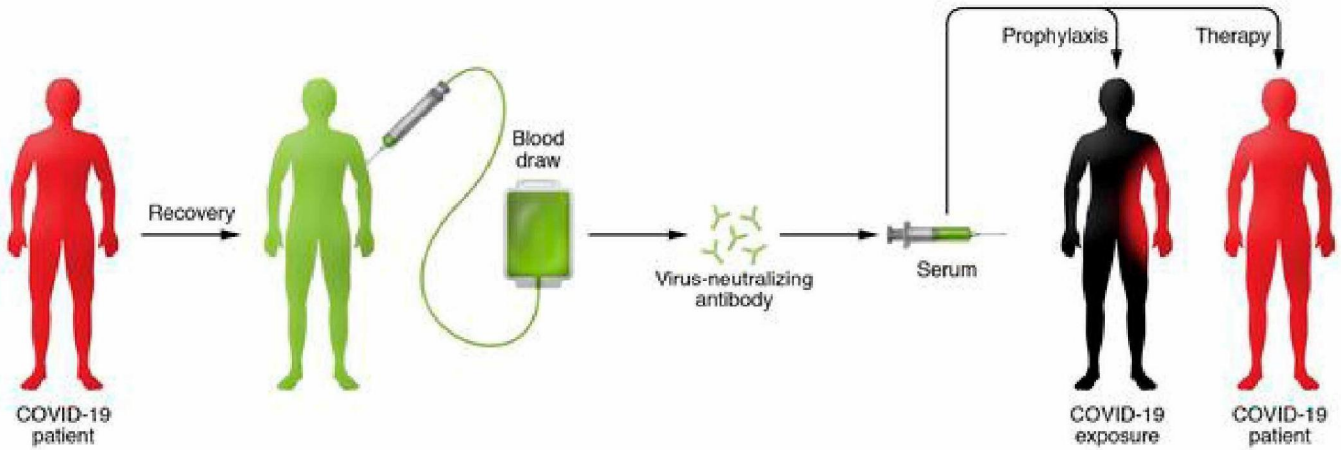
- are being evaluated for prevention of COVID-19. The first vaccine to undergo preliminary study in humans in the United States uses a messenger RNA platform to result in expression of the viral spike protein in order to induce an immune response

Investigational agents

- Remdesivir
- Chloroquine/hydroxychloroquine
- Tocilizumab, Lopinavir-ritonavir

Convalescent plasma infusion

The use of convalescent plasma in COVID-19



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Convalescent plasma in COVID-19

Principle:

- Passive antibody therapy, which involves the administration of antibodies against a given agent to a susceptible individual for the purpose of preventing or treating an infectious disease due to that agent.

Mechanism:

- the anticipated mechanism of action by which passive antibody therapy would mediate protection is **viral neutralization**, but also antibody-dependent cellular cytotoxicity and/or phagocytosis.

Experiences in the past:

- Historically, developed in 1890 as the only means of treating certain infectious diseases prior to the development of antimicrobial therapy in the 1940s
- In the early twentieth century convalescent sera was used to stem outbreaks of viral diseases such as poliomyelitis, measles, mumps and influenza. A retrospective meta-analysis of eight studies on the use of convalescent sera involving 1703 patients during the 1918 H1N1 influenza virus pandemic suggested that those who received serum had lower mortality.

Recent experiences in using convalescent plasma

2009–2010 H1N1 influenza virus pandemic,

- convalescent serum antibody preparations obtained by apheresis were used to treat individuals with severe H1N1 2009 infection requiring intensive care . Serum-treated individuals manifested reduced respiratory viral burden, serum cytokine responses, and mortality.

2013 West African Ebola epidemic,

- A small nonrandomized study in Sierra Leone revealed significantly longer survival for those treated with convalescent whole blood relative to those who received standard treatment

H5N1 and H7N9 avian flu outbreaks

- anecdotal use of convalescent sera was effective, with all patients surviving.

Convalescent plasma for SARS and MERS

The largest study involved the treatment of 80 patients with SARS in Hong Kong. Patients treated before day 14 had improved prognosis defined by discharge from hospital before day 22, consistent with the notion that earlier administration is more likely to be effective. In addition, those who were PCR positive and seronegative for coronavirus at the time of therapy had improved prognosis.

Three patients with SARS in Taiwan were treated with 500 mL convalescent serum, resulting in a reduction in serum virus titer, and each survived.

Three patients with MERS in South Korea were treated with convalescent serum, but only two of the recipients had neutralizing antibody in their serum

The latter study highlights a challenge in using convalescent sera, namely, that some who recover from viral disease may not have high titers of neutralizing antibody.

An analysis of 99 samples of convalescent sera from patients with SARS showed that 87 had neutralizing antibody, with a geometric mean titer of 1:61.

Convalescent plasma during current outbreak

Case series of 5 critically ill patients with laboratory-confirmed COVID-19 and acute respiratory distress syndrome (ARDS).

- Administration of convalescent plasma containing neutralizing antibody was followed by improvement in their clinical status.

The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study

- 10 severe laboratory confirmed patients, one dose of 200 mL convalescent plasma with the neutralizing antibody titers > 1:640
- the level of neutralizing antibody increased rapidly up to 1:640 in five cases, in four cases maintained at a high level (1:640).
- The clinical symptoms and laboratory data were significantly improved within 3 days. Radiological examinations showed varying degrees of absorption of lung lesions within 7 days.
- The viral load was undetectable after transfusion in seven patients who had previous viremia. No severe adverse effects were observed.

Potential risks

Known risks for all plasma transfusions

- Non-specific and related to administration of human plasma: TTI, TACO, TRALI, ABO incompatibility, hypersensitivity due IgA deficiency, febrile reactions, ...

Theoretical risks for convalescent plasma

- **Antibody-dependent enhancement** (**ADE**) occurs when non-neutralizing antiviral proteins facilitate virus entry into host cells, leading to increased infectivity in the cells
- **Attenuation (suppression) immune response – antibodies** may prevent disease in a manner that attenuate the immune response, leaving such individuals vulnerable to subsequent reinfection

Conditions for deployment of convalescent plasma use

(i) availability of a population of donors who have recovered from the disease and can donate convalescent plasma;

(ii) blood banking facilities to process the plasma donations;

(iii) availability of assays, including serological assays, to detect SARS-CoV-2 in serum and virological assays to measure viral neutralization;

(iv) virology laboratory support to perform these assays;

(v) prophylaxis and/or therapeutic protocols, which should ideally include randomized clinical trials to assess the efficacy of any intervention and measure immune responses;

(vi) data collection

(vii) regulatory compliance, including institutional review board approval, which may vary depending on location.

General Regulatory Considerations - WHO

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

Standards for product manufacturing should maximize safety of donors and recipients

Criteria for patients to be treated

General considerations for plasma products are applicable

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

Potential use of small scale immunoglobulin concentrates

Feasibility of large scale production including manufacture of purified immunoglobulins

Instead of conclusion

Human convalescent plasma is an option for prevention and treatment of COVID-19

Potential benefits related to use of convalescent plasma for treatment of COVID-19 outweigh known and theoretical risks related to plasma application

As we are in the midst of a pandemic, and in the absence of any other therapeutic or prophylactic means, it might be essential to begin with the emergency use of convalescent plasma as soon as possible.