COVID-19 convalescent plasma – status and prospects

5.1.2e 5.1.2e, Stockholm, 09 February 2021

COVID-19 convalescent plasma (CCP) - main drivers

- Disease impact: pandemic spread, disease severity and mortality rate
- Lack of effective therapy or vaccination
- Historical experiences
- Immediate availability and growing pool of convalescent patients
- Promising outcomes of initial case series in humans and animal studies
- Open questions: safety and efficacy

Initial phase

The development of donation and production protocols of CCP:

- Donor recruitment (general vs. targeted)
- Donor selection (NAT test positive, symptoms only, Ab test)
- Donation (plasmapheresis vs. whole blood, content of neutralizing Abs)
- Processing (pathogen reduction, pooling, product volume)
- Product labelling

Regulatory preconditions

- Product authorisation
- Clinical use authorisation

Research:

- Initiation of clinical studies non-randomized and randomized

Use of CCP

- Compassionate emergency use, within clinical studies including expanded access protocol (USA)

Initial phase

Safety

A number of non-randomized studies and enrolling a large number of patients showed that frequency of adverse effects after CCP doesn't differ from know frequency after fresh frozen plasma therapy

Strong signal towards acceptable safety risks. Antibody Dependent Enhancement has after CCP has not been observed.

Efficacy

Patients in various clinical stages (mostly sever or critically ill) received various volumes of CCP containing various titer of neutralizing Abs at various time after symptom onset or admission.

Week signal towards reduced mortality if a high-titer nAbs CCP is applied to non-intubated patients in the early stage of disease although some studies showed no benefit

Current phase

CCP product

- Alternative products suggested:
  - Pooled products.
  - Plasma Cryoprecipitate Reduced (Cryosupernatant)
  - Affinity Column Preparation of Antibody Hyperconcentrate
- High-titer neutralizing antibodies only CCP
- Surrogate neutralizing Ab tests proposed to discriminate high- and low-titer neutralizing Abs CCP
- WHO Ab test standards developed
- Donation CCP and vaccination

Study results evaluated

- Several randomized controlled studies – reports available
- Systematic reviews and meta analyses of aggregated data using fixed effect or random effect model
- New studies launched

Donation CCP and vaccination

ECDC, COVID-19 and the safety of SoHO supply, **revised** second Update:

- According to EU Directives, after vaccination with attenuated viruses (e.g. replication competent virus vector-based vaccines, live-attenuated virus vaccines) SoHO donors must be deferred for four weeks. Individuals vaccinated with inactivated viruses or vaccines that do not contain live agents (i.e. **mRNA vaccines, non-replicating/replication deficient virus vector-based vaccines** and protein subunit vaccines) may be accepted as SoHO donors if they feel well.

Deferral of a donor after receiving currently registered COVID-19 vaccines in the EU is not required.

Donation CCP and vaccination

According to FDA:

Individuals who have never been infected with COVID-19 and have received a COVID-19 vaccine are not eligible to donate CCP:

- This is to ensure that CCP collected from donors contains sufficient antibodies directly related to their immune response to COVID-19 infection.
- Administration of COVID-19 vaccines for the purpose of boosting immunity of convalescent plasma donors would need to be conducted within a clinical trial.
- (Com. DD: Precautionary measure as because limited knowledge on the possibility of reinfection in vaccinated individuals especially with the lower content of Abs)

Recovered COVID-19 patients who are eligible to donate CCP and also receive an investigational, authorized or licensed COVID-19 vaccine after recovery are eligible to donate only if they:

- had symptoms of COVID-19 and a positive test result
- received the COVID-19 vaccine after diagnosis of COVID-19, AND
- are within 6 months after complete resolution of COVID-19 symptoms.

WHO standards

WHO/BS.2020.2403 Establishment of the WHO International Standard and Reference Panel for anti-SARS-CoV-2 antibody

- WHO International Standard of 250 IU/ampoule for neutralising antibody activity and 250 IU/ampoule for binding antibody activity.
- The availability of an International Standard (IS) for antibodies facilitates the standardisation of SARS-CoV-2 serological methods and allow for comparison and harmonisation of datasets across laboratories.

CCP - possible mechanism of action

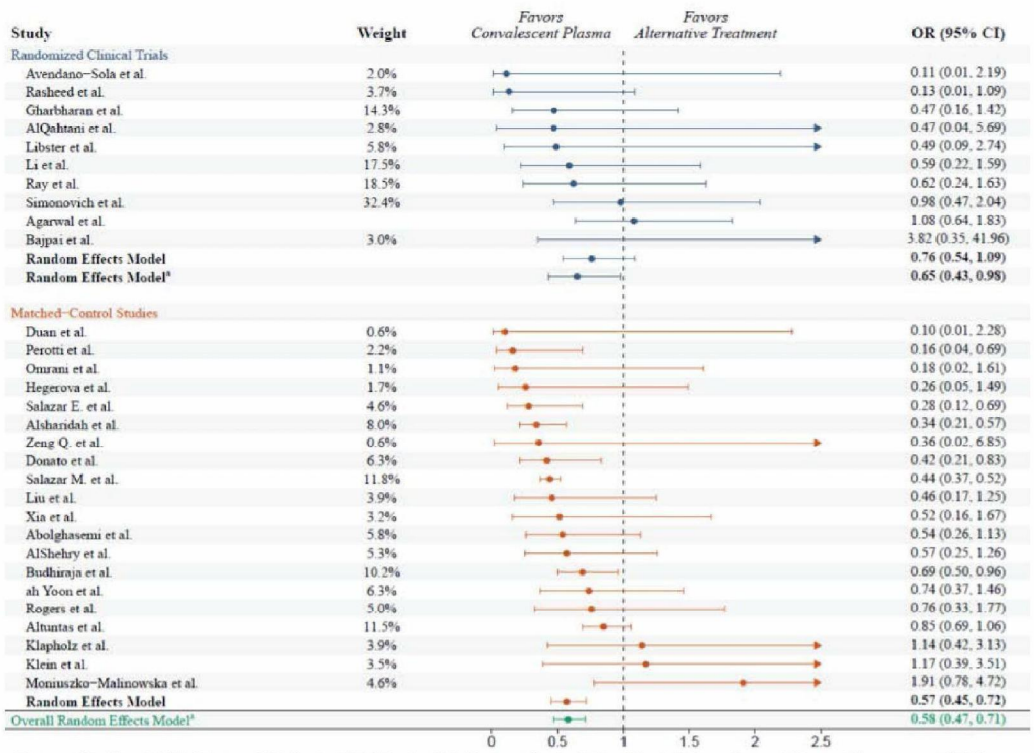
Possible mechanism of action= anti- SARS-CoV-2 neutralizing antibodies

- **Antiviral effects**
- **Immunomodulatory effects**
- **Modulation of the hypercoagulable state**

SARS-CoV-2 neutralizing antibodies

- **CCP contains SARS-CoV-2 neutralizing antibodies (nAb), which have an antiviral effect (prevent the replication of the virus by blocking attachment to the host cell)**
  - Robbiani DF, et al. Convergent antibody responses to SARS-CoV-2 in convalescent individuals. Nature. 2020 2020/08/01;584(7821):437-42.
  - Klein SL, et al. Sex, age, and hospitalization drive antibody responses in a COVID-19 convalescent plasma donor population. J Clin Invest. 2020 Nov 2;130(11):6141-50.
- **Administration CCP containing nAbs increases SARS-CoV-2 clearance in COVID-19 patients including immunocompromised individuals.**
  - Liu Z. Errors in Trial of Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients with Severe and Life-threatening COVID-19. *JAMA - J Am Med Assoc.* 2020;324(5):518-519.
  - Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci U S A.* 2020;117(17):9490-9496.
- **Decreased viral load reduces the alveolar tissues damage and consequently the inflammatory response and thus lessens a likelihood that an over-exuberant immune response will cause the disease progression into severe and critical stage.**
- **Administration of human CCP is protective against SARS-CoV-2 infection- animal studies**

Systematic review and meta analysis – reduced mortality after CCP treatment



Klassen SA, Senefeld J, Johnson PW, Carter RE, Wiggins CC, Shoham S, et al. The Effect of Convalescent Plasma Therapy on COVID-19 Patient Mortality: Systematic Review and Meta-analysis. medRxiv. 2021:2020.07.29.20162917.

OR >1 indicates increased mortality

OR <1 indicates decreased mortality

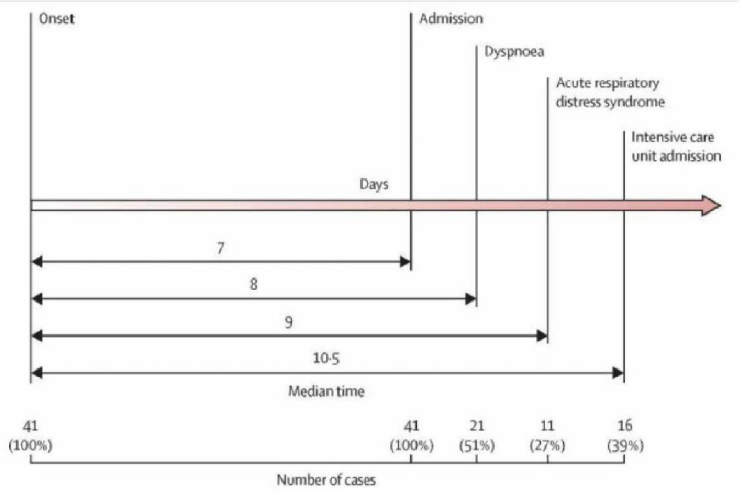
Current phase - CCP efficacy

- **CCP is not effective in the severe and critically ill patients**
  - REMAP-CAP trial has paused the enrolment of critically ill COVID-19 patients, though continued with recruitment of patients with moderate disease.
  - Joyner M, Carter R, Senefeld J, et al. Convalescent plasma antibody levels and the risk of death from covid-19. N Engl J Med. doi:10.1056/NEJMoa2031893.

  Possible explanation
  - Main action of neutralizing Ab in CCP is an antiviral effect. Reducing viral load by giving CCP to severe or critical patients may not prevent disease progression and reduce mortality because a hyperinflammatory response with cytokine hyperproduction rather than virus spread are major pathophysiological changes responsible for clinical picture.
- **CCP transfusion in mild and moderate patients is under clinical investigation**

Current phase CCP efficacy

Early transfusion (within 3 days of hospital admission) of higher-titer CCP is associated with lower patient mortality



Klassen SA, et al. The Effect of Convalescent Plasma Therapy on COVID-19 Patient Mortality: Systematic Review and Meta-analysis. medRxiv. 2021:2020.07.29.20162917.

Possible explanation

The mean time between admission to the hospital and progression to severe stage of disease is 3 (5) days.

During this period, high titers of neutralizing antibodies in the transfused CCP, together with the patient's antibodies, may be sufficient to reduce the viral load below levels leading to a hyperinflammatory response and disease progression.

Current phase CCP efficacy

- **CCP containing a high-titer neutralizing antibodies was associated with decrease mortality**
  - Libster R, et al. Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults. New England Journal of Medicine. 2021.
  - **Possible explanation**
  - A high nAb titer in transfused CCP is required to increase antibody levels and significantly reduce viral load
- **Proposed actions**
  - Standardize methods for determining the titer of neutralizing antibodies
  - Define high-titer discriminating value
  - Define minimum therapeutically effective dose and adjust dose per recipient body weight
  - Discourage the use of low-titer CCP

FDA - ELISA tests and qualifying values for high-titer nAbs in CCP

Tests Acceptable for Use in the Manufacture of High Titer COVID-19 Convalescent Plasma		
Manufacturer (listed alphabetically)	**Assay**	**Qualifying Result**
Abbott	SARS-CoV-2 IgG (ARCHITECT and Alinityi)	Index (S/C) ≥ 4.5
Beckman Coulter	Access SARS-CoV-2 IgG	S/CO ≥ 3.3
EUROIMMUN	Anti-SARS-CoV-2 ELISA (IgG)	Ratio ≥ 3.5
GenScript	cPass SARS-CoV-2 Neutralization Antibody Detection Kit	Inhibition ≥ 68%
Kantaro	COVID-SeroKlir, Kantaro Semi-Quantitative SARS-CoV-2 IgG Antibody Kit	Spike ELISA > 47 AU/mL
Mount Sinai	COVID-19 ELISA IgG	Spike ELISA titer ≥ 1:2880
Ortho	VITROS Anti-SARS-CoV-2 IgG	S/C ≥ 9.5
Roche	Elecsys Anti-SARS-CoV-2 S	≥ 132 U/mL
Siemens	ADVIA Centaur SARS-CoV-2 IgG (COV2G)	Index ≥ 4.8

https://www.fda.gov/media/141477/download

Upcoming phase

- Standard protocol for convalescent plasma donation and preparation
- Convalescent plasma monograph (in Europe, EDQM Guide)
- CCP approved as a standard treatment of COVID-19 moderately ill patients including immunodeficient patients
- Affordable especially in middle and underdeveloped countries
- Prophylaxis for specific population
- Source plasma for the production of anti SARS-CoV-2 hyperimmune gamaglobulins