Convalescent plasma to treat COVID-19 and associated studies

Pierre Tiberghien
Etablissement Français du Sang / Université de Franche-Comté

On behalf of the
French COVID-19 convalescent plasma and associated studies Working Group

REACTing Inserm / IHU Méditerranée Infection / AP-HP / EFS

- The Coronavirus disease 2019 (COVID-19) viral pneumonia is now a world-wide pandemic.
- To date, no specific treatment has been proven to be effective for COVID-19.
- In this context, the therapeutic potential associated with convalescent plasma merits to be explored.

- Convalescent plasma treatment, i.e. passive polyclonal antibody administration to provide immediate immunity, has been used to improve the survival rate of patients with severe acute respiratory syndromes of viral etiology, including SARS-CoV infection in 2003.

- Experience from prior outbreaks with other coronaviruses, such as SARS-CoV-1, shows that such convalescent sera contain neutralizing antibodies to the relevant virus

- A number of studies, unfortunately all inadequately controlled for bias, have reported positive outcomes, including decreased mortality in the so-called Spanish Influenza A (H1N1) infections in 1915-1917 , the more recent Influenza A (H1N1)pdm09 infections in 2009/2010 , and more importantly here, SARS-CoV infections in 2003.

- Studies involving COVID-19 convalescent plasma are underway in China and being considered in several EU countries. EU Blood establishments are coordinating to collect and prepare convalescent plasma for clinical use Europe-wide.

- Prior systematic analysis in 2015 (Mair-Jenkins J et al, J Infect Dis. 2015) reported improved mortality after SARS-CoV – infected patients received various amount of convalescent plasma. Notably:
  - A small retrospective case-comparison study (19 vs 21 patients) showed a case fatality rate reduction after convalescent plasma treatment of 23% (95% CI: 6%-42%, p=0,049).
  - Also, a case series including 80 treated patients reported an overall mortality rate of 12,5% in severe deteriorating SARS-CoV infected patients while the overall SARS-related mortality rate in Hong-Kong was 17% during the SARS epidemic in 2003
    - Recipients of convalescent plasma early on (before seroconversion) vs later were found to have a better outcome (similar result after adjusting for covariables, with however a high risk of bias).
- Up to 2015, no serious adverse events were reported with convalescent plasma (in over 700 patients). Since then, 2 cases of suspected TRALI (without anti-HLA/HNA Ab have been reported.
- Antibody-dependent enhancement early-on in the disease may be an issue
  - Early endogenous Ab response may be pathogenic (viral spread? / Th2 inflammatory response?)
  - Late Ab response may differ significantly (enhanced affinity?, different specificities?)
- Initial results involving convalescent plasma administration in severe COVID-19 patients are encouraging, despite the absence adequate controls (Shen et al, JAMA, February 27th)

Working hypothesis: early administration of convalescent plasma containing high titer neutralizing Abs may inhibit viral entry and replication and consequently blunt an early “pathogenic” endogenous Ab response.

Two issues for us:

- Making COVID-19 convalescent plasma available
- Evaluating the safety and efficacy of convalescent plasma to treat COVID-19

Making convalescent plasma available:

- Convalescent patients will be identified through the French COVID-19 cohort, hospitals data-bases such as COVIDOM as well as direct information to convalescent patients when leaving the hospital, or at time of diagnosis for outpatients
- Convalescent patients will be invited to undergo plasma apheresis at an EFS blood collection site.
- The apheresis procedure will be performed per standard procedures. A mean of approximately 600 ml of plasma will undergo routine microbiological testing and pathogen reduction treatment (Intercept, Cerus).
- An adequate immune profile (anti-SARS-CoV-2 neutralizing Ab titer >=40) as well a negative RT-PCR will be verified
- Once treated and qualified, plasma will be cryopreserved and made available clinical use
- Appropriate regulatory and ethical approvals have been obtained.
- Processes for donor invitation and plasma collection, qualification, treatment and issuing are being finalized.
- EFS will start collecting and making available convalescent plasma on April 7th in the regions Ile-de-France, Grand Est and Bourgogne-Franche-Comté.

Evaluating the safety and efficacy of convalescent plasma:

NESTED TRIAL IN CORIMMUNO-19: EFFICACY OF HYPERIMMUNE PLASMA FOR PATIENTS WITH COVID-19

THE COVIPLASM TRIAL

Promoter: AP-HP

Principal investigator: Pr Karine Lacombe, Sorbonne Université, IPLESP UMR-S1136

Associated investigators :

- Pr Pierre Tiberghien, Etablissement Français du Sang, Université de Franche Comté, UMR 1098 RIGHT
- Dr Pascal Morel, Etablissement Français du Sang
- Pr Xavier de Lamballerie, Institut Hospitalo-Universitaire Méditerranée Infection, UMR IRD 190 Emergences des pathologies virales

CENTRE DE METHODOLOGIE ET DE GESTION: URC Lariboisière - St Louis, avec délégation de promotion à l'URC-EST (Dr Laurence Berard)

ANALYSE STATISTIQUE: Dr Raphael Porcher, Centre d'Epidémiologie Clinique**,** Hôpital Hôtel Dieu et par délégation M. Lambert Assoumou, IPLESP Inserm UMR-S1136

Partners : Services de maladies infectieuses et de médecine interne, Groupe Hospitalier Sorbonne-Université, AP-HP, Etablissement Français du Sang, IHU Méditerranée Infection, REACTing Inserm.

Convalescent plasma

Convalescent donor selection

- Standard eligibility criteria, including a delay of 14 days since end of COVID-19 symptoms (fever, dyspnea)
- Potential variations to be possibly submitted to ANSM for approval :
  - Convalescent donors less than 4 months since hospitalization in an intensive care unit?
  - Convalescent donors previously transfused?
  - Others?

Apheresis : standard procedure, volume adapted to BMI
Frequency : up to 3 times with a minimum15 days interval (per standard regulation)

Donor qualification:

- standard (including HEV RNA and anti-HLA Ab for women with children)
- SARS CoV-2 RT-PCR and neutralizing activity titer (>= 1/40)
- Specific questionnaire pertaining to prior COVID-19 disease (diagnosis, date of first symptoms, severity, date of last symptoms)

Plasma: pathogen reduced and cryopreserved for use as:

- Convalescent plasma (neutralizing titer > 1/40)
- Standard plasma (neutralizing a < 1/40)

Nb of patients included :

- Per methodology CORIMMUNO-19 cohort
- 30 treated patients, renewed as needed, pending assessment every 10 patient, same number of controls
- Additional treated patients, per assessment

Inclusion Criteria:

Patients included in the CORIMMUNO-19 cohort with the specific following criteria:

- Mild severity (grade 4 or 5) as described in the WHO scale
- Hospitalized and less than 10 days after onset of symptoms

Available ABO compatible convalescent plasma

Plasma administration:

Two units of plasma (400-440 ml/day) as soon as possible, 2 days in a row, at the latest on day 10 and 11 after onset of symptoms.

Endpoints of the trial

Efficacy endpoints

Primary endpoints:

1. Survival without needs of ventilator utilization (including non- invasive ventilation) or other immunomodulatory agents at day 14.
2. Early end point : WHO progression scale >=7 at day 4 after plasma transfusion

Secondary end-points: not detailed here

Safety endpoints

Occurrence of severe adverse events known to be associated with plasma transfusion

Occurrence of systemic and/or local (lungs) inflammation associated with convalescent plasma transfusion

WHO progression scale

OMS Progression scale	Descriptor	Score
Uninfected	Uninfected; non viral RNA detected	0
Ambulatory	Asymptomatic; viral RNA detected	1
Ambulatory	Symptomatic; Independent	2
Ambulatory	Symptomatic; Assistance needed	3
Hospitalized : mild disease	Hospitalized; No oxygen therapy	4
Hospitalized : mild disease	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized : severe disease	Hospitalized; oxygen by NIV or High flow	6
Hospitalized : severe disease	Intubation and Mechanical ventilation, pO2/FIO2>=150 OR SpO2/FIO2>=200	7
Hospitalized : severe disease	Mechanical ventilation, (pO2/FIO2<150 OR pO2/FIO2<200) OR vasopressors (norepinephrine >0.3 microg/kg/min)	8
Hospitalized : severe disease	Mechanical ventilation, pO2/FIO2<150 AND vasopressors (norepinephrine >0.3 microg/kg/min), OR Dialysis OR ECMO	9
Death	Dead	10

Calendar

- ANSM and ethics approval : March 3rd, 2020
- First patients included: April 14th, 2020
- Last patients included: April 28th, 2020

In parallel: potential "compassionate" use?

Pending plasma availability, ANSM approval and appropriate monitoring

Subsequently:

- Positive result:
  - Nation-wide provision of convalescent plasma
  - Further assessment of efficacy
    - Administration a later times point?
    - Combination with anti-inflammatory molecules
- Negative result:
  - Further clinical trials assessing different treatment modalities

Financial support:

- APHP and EFS
- REACTing
- Sorbonne University / PHRC / FRM (submitted or under consideration)

SARS-CoV-2 seroprevalence studies

Coordination for EFS: Pierre Gallian

Material:

- 10 000 blood donations daily nation-wide
- At every donation: 1 ml x 2 cryopreserved for 3 years

Use of such material to:

- Assess seroprevalence **nation-wide** for any infectious agent generating an Ab response
- At **any time period** over the last 3 years up to today
- Urgent mode « flash study » to **acutely inform health-related policies**
- « Standard mode » **epidemiological assessments**
  - Before and after and epidemic / pandemic
  - Combined with donor information (risk factors, vaccination, disease, …)

Prior studies:

EFS / IHU Méditerranée Infection / Santé Publique France:
Hepatitis E, Chikungunya, HIN1 influenza, Zika

Currently: Flash study, with Institut Pasteur (Arnaud Fontanet)
Planned: « standard mode » studies, with IHU Marseille (Xavier de Lamballerie)

Financial support : EFS, REACTing, ANR (submitted), PHRC and FRM (under consideration)