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Note: DOCUMENT TRANSLATION WITH DeepL

Opinion of the AVATHER group on the role of COVID Convalescent Plasma (PCC) in the treatment of COVID19 in immunocompromised patients

- Although the studies available to date do not make it possible to recommend the use of PCCs as an early treatment for COVID19, several studies published to date suggest a possible benefit of PCC treatment for immunocompromised patients with prolonged replication of SARS-CoV-2.
- **However, the AVATHER group considers that the level of evidence is not sufficient to recommend the routine use of PCCs in this situation,** in line with the main international recommendations (Appendix 1).
- Nevertheless
  1) because of the therapeutic impasse in some of these patients,
  2) due to the rather positive signals from published studies,
  3) in the absence of any major deleterious effect observed to date,
  4) pending the results of clinical trials
  5) and in line with some of the international recommendations (Appendix 1)

  the impact of PCCs must continue to be evaluated in a clinical research context, using a standardised, protocolised approach (particularly with regard to indications, conditions of use with standardised assessment of neutralising capacity against circulating strains, and virological and clinical efficacy criteria), and including an analysis of the data already available (particularly from the Temporary Use Protocol).

- This also means **maintaining a production and supply chain that** takes into account the need to update available plasma batches according to the epidemiology of circulating variants. This means that the collection and immunological qualification of PCC batches must continue.
- In the longer term, it would be ideal to have access to **purified human immunoglobulins** derived from these PCCs, in order to better control the pharmacologically active component of these plasmas. The Group therefore calls on the public authorities to encourage the EFS and laboratories with expertise in the fractionation of stable blood products to work together to consider setting up a production chain for purified human immunoglobulins specific to SARS-CoV-2. As well as providing an immediate response to a medical need that is insufficiently met, such an initiative would play a structuring role in preparing for future epidemic threats.

Appendix 1: Overview of recommendations on the use of convalescent plasma in the treatment of COVID-19

from 1er august 2023

NIH Covid treatment Guidelines

https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/covid-19-convalescent-plasma/

Last Updated: July 21, 2023

Recommendations

Patients Who Are Immunocompromised

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of high-titer CCP for the treatment of COVID-19 in hospitalized or nonhospitalized patients who are immunocompromised.
- Some people who are immunocompromised have prolonged, symptomatic COVID-19 with evidence of ongoing SARS-CoV-2 replication. Without definitive data, some Panel members would use 1 or more of the following treatment options:
    - Longer and/or additional courses of ritonavir-boosted nirmatrelvir (Paxlovid)
    - Longer and/or additional courses of remdesivir
    - High-titer CCP from a vaccinated donor who recently recovered from COVID-19 likely caused by a SARS-CoV-2 variant similar to the variant causing the patient's illness

Patients Who Are Immunocompetent

- The Panel **recommends against** the use of CCP for the treatment of COVID-19 in hospitalized patients who are immunocompetent **(A1)**
- There is insufficient evidence for the Panel to recommend either for or against the use of high- titer CCP for the treatment of COVID-19 in nonhospitalized patients who are immunocompetent.

European Myeloma Network consensus

Leukemia 28 July 2023 https://www.nature.com/articles/s41375-023-01974-1

we believe that although convalescent plasma may be an option for subgroups of patients with COVID- 19, the available data do not support its use in patients with multiple myeloma in the post-pandemic era. That is why EMN does not recommend convalescent plasma in patients with multiple myeloma and COVID-19 outside of clinical trials.

European Conference on Infections in Leukemia (ECIL-9)

(updated 17 July 2023, Leukemia https://www.nature.com/articles/s41375-023-01938-5)

The data available for high titer of convalescent plasma (CVP) does not support its role in the routine treatment of mild/moderate COVID-19. Considering the polyclonal protection given by CVP, less influenced by protein-S mutations which led to the loss of activity of MoAbs, CVP might be useful in immunocompromised patients, in addition to antivirals.

IDSA

(https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#Recommendations13-15:Convalescentplasma)

Section last reviewed and updated on 2/22/2023

Recommendation 13: Among immunocompetent patients hospitalized with COVID-19, the IDSA guideline panel recommends against COVID-19 convalescent plasma (Strong recommendation, Moderate certainty of evidence).

Recommendation 14: Among immunocompromised patients hospitalized with COVID-19, the IDSA guideline panel suggests against the routine use of COVID-19 convalescent plasma. (Conditional recommendation, very low certainty of evidence)

Remarks:

- *Patients, particularly those who do not qualify for other treatments, who place a higher value on the uncertain mortality reduction and a lower value on the potential adverse effects of convalescent plasma would reasonably select convalescent plasma.*

Recommendation 15: Among ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease who have no other treatment options*, the IDSA guideline panel suggests FDA-qualified high-titer COVID-19 convalescent plasma within 8 days of symptom onset rather than no high-titer COVID-19 convalescent plasma. (Conditional recommendation†, Low certainty of evidence**)**

**Other options for treatment and management of ambulatory patients include nirmatrelvir/ritonavir and three-day treatment with remdesivir Patient-specific factors (e.g., symptom duration, renal insufficiency or other contraindications, drug interactions) as well as logistical challenges, infusion capacity, and product availability should drive decision-making regarding choice of agent. Data for combination treatment do not exist in this setting.*

†The *guideline panel concluded that the desirable effects outweigh the undesirable effects, though uncertainty still exists, and most informed people would choose the suggested course of action, while a substantial number would not.*

FDA

https://www.fda.gov/media/136798/download

January 7, 2022, and intended to remain in effect until November 7, 2023

Because convalescent plasma for the treatment of COVID-19 has not yet been approved for use by FDA,5F it is an investigational product.

The emergency use of COVID-19 convalescent plasma is not authorized under the EUA unless it is consistent with, and does not exceed, the terms of the Letter of Authorization, including the Scope of Authorization and Conditions of Authorization

Criteria for Issuance of Authorization

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

it is reasonable to believe that the known and potential benefits of COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies, when used for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in either the outpatient or inpatient setting, and used in accordance with this Scope of Authorization (Section II), outweigh its known and potential risks.

Appendix A: Table of Tests Acceptable for Use in the Manufacture of COVID-19 Convalescent Plasma with High Titers of Anti-SARS-CoV-2 Antibodies

Tests Acceptable for Use in the Manufacture of COVID-19 Convalescent Plasma with High Titers of Anti-SARS-CoV-2 Antibodies			
Manufacturer (listed alphabetically)	**Assay**	**Qualifying Result**	**Date of Listing under this EUA**
Abbott	AdviseDx SARSCoV-2 IgG II (ARCHITECT and Alinity i)	≥ 1280 AU/mL	December 28, 2021
Diasorin	LIAISON SARS-CoV-2 TrimericS IgG	≥ 87 AU/mL	December 28, 2021
EUROIMMUN	Anti-SARS-CoV-2 S1 Curve ELISA (IgG)	>55 RU/mL	February 9, 2022
GenScript	cPass SARS-CoV-2 Neutralization Antibody Detection Kit	Inhibition ≥ 80%	December 28, 2021
Kantaro	COVID-SeroKlir, Kantaro Semi-Quantitative SARS-CoV-2 IgG Antibody Kit	Spike ELISA > 69 AU/mL	December 28, 2021
Ortho	VITROS Anti-SARS-CoV-2 IgG Quantitative Reagent Pack	>200 BAU/mL	December 28, 2021
Roche	Elecsys Anti-SARS-CoV-2 S	> 210 U/mL	December 28, 2021

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance Therapeutics for people with COVID-19

21 February 2023

https://www.nice.org.uk/guidance/ta878/documents/final-appraisal-determination-document

Plasma from convalescents not mentioned

ESCMID

Guidelines: update on treatment for patients with mild/moderate disease

Volume 28, Issue 12, December 2022, Pages 1578-1590

https://www.sciencedirect.com/science/article/pii/S1198743X22004293?via%3Dihub

Plasma from convalescents not mentioned