Avis du groupe AVATHER sur la place du Plasma de Convalescents COVID (PCC) dans le traitement de la COVID19 chez les patients immunodéprimés

- Si les études disponibles à ce jour ne permettent pas de recommander l'utilisation des PCC en traitement précoce de la COVID19, plusieurs études publiées à ce jour suggèrent un possible bénéfice de ce traitement par PCC des patients immunodéprimés ayant une réplication prolongée du SARS-CoV-2.
- **Le groupe AVATHER considère cependant que le niveau de preuve n'est pas suffisant pour que la recommandation puisse être faite d'utiliser en pratique courante les PCC dans cette situation,** avis en cohérence avec les principales recommandations internationales (Annexe 1).
- Néanmoins
  1) du fait de la situation d'impasse thérapeutique chez certains de ces patients,
  2) du fait des signaux plutôt positifs des études publiées,
  3) en l'absence d'effet délétère majeur observé à ce jour,
  4) dans l'attente de résultats d'essais cliniques
  5) et en cohérence avec certaines des recommandations internationales (Annexe 1)

  l'impact des PCC doit pouvoir continuer à être évalué dans un cadre de recherche clinique, avec une démarche protocolisée et standardisée (notamment quant aux indications, aux conditions d'utilisation avec évaluation standardisée de la capacité neutralisante vis-à-vis des souches en circulation, et aux critères d'efficacités virologiques et cliniques), et incluant une analyse des données déjà disponibles (notamment du Protocole d'Utilisation Temporaire).

- Ceci implique aussi le **maintien d'une filière de production et d'approvisionnement** prenant en compte la nécessaire actualisation des lots de plasma disponibles en fonction de l'épidémiologie des variants circulants Ceci nécessite que la collecte et la qualification immunologique des lots des PCC se poursuivent.
- A plus long terme, l'idéal serait de pouvoir disposer d'**immunoglobulines humaines purifiées** issues de ces PCC, afin de mieux contrôler la composante pharmacologiquement active de ces plasmas. Le groupe appelle donc de ses vœux une concertation, sous l'égide des pouvoirs publics, entre l'EFS et les laboratoires maîtrisant le fractionnement en produits sanguins stables, afin de considérer la mise en place une filière de production d'immunoglobulines humaines purifiées spécifiques du SARS-CoV-2. Au-delà de la réponse immédiate à un besoin médical insuffisamment pourvu, une telle initiative jouerait un rôle structurant dans la perspective de la préparation à de futures menaces épidémiques.

Annexe 1 : état des lieux des recommandations sur l'utilisation des plasmas de convalescents dans le traitement de la COVID-19

en date du 1er aout 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 juillet 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)

(update 17 juillet 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 Février 2023

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

Plasma de convalescents non mentionnés

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 de convalescents non mentionnés