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AVATHER GROUP MEETING

Strategic therapeutic positioning Plasmas for convalescents COVID19 and Sotrovimab

24 January 2022

Participants

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Permanent guests: Alban Dhanani (ANSM), Clotilde Latarche (MSS)
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Introduction

The AVATHER group met on 24 January 2023 to discuss the impact of recent data concerning the possibility of positioning COVID19 in the therapeutic strategy in the early phase:

- COVID19 convalescent plasma (PC),
- sotrovimab (Xevudy),®

in the therapeutic strategy for early-stage COVID19 in the current epidemic context, as a third-line alternative to nirmatrelvir/ritonavir (Paxlovid®) and remdesivir (Veklury®), in people at high risk of progressing to a severe form of COVID-19.

The role of convalescent plasma in the early treatment of SARS-CoV-2 infection

The data in the literature show divergent results regarding the efficacy of treating COVID-19 with PC.

With regard to the administration of PC in the early phase of COVID-19, which is the subject of this opinion, the results of 5 randomised trials and 2 meta-analyses are now available:

- Libster R, et al. NEJM 2021 - treatment within 72 hours of onset of symptoms. Target population: elderly subjects (> 65 years), prior to vaccination.
  Benefit on progression to severe forms (RR: 0.52 (0.29-0.94), with a clearer effect when the plasma has a high neutralising antibody titre.
  Possible bias: more patients aged ≥75 years in the placebo group than in the CP group (60% vs. 50 %).

- Sullivan DJ, et al. NEJM 2022 - treatment within 5 days of onset of symptoms. Mainly unvaccinated population, few elderly subjects. No immunocompromised patients.
  Reduced risk of hospitalisation (2.9% vs 6.3%, p= 0.005) but low risk of progression to forms of the disease requiring hospitalisation, particularly in non-vaccinated patients (80% of the population is vaccinated).

- Korley FK, et al. NEJM 2021 - treatment within 3-4 days of onset of symptoms. Population: subjects at risk of disease progression to more severe forms (elderly patients or patients with comorbidities, but not immunocompromised patients), most of whom have not been vaccinated or have only been partially vaccinated. Limitation: no indication of the neutralising antibody titre of the PC administered (although it is likely that FDA criteria are applied, with a NAb rate ≥ 1/640).
  □ No difference in the primary endpoint (hospitalisation, emergency department access or death without hospitalisation) between the treatment and placebo groups.

- Alemany A, et al. Lancet Resp Med 2022 - treatment within 7 days of symptom onset. PC treated with methylene, EUROIMMUN ELISA titre ≥ 6 (but neutralising titre not known). Population: patients at risk of severe forms; 50% smokers, 24% obese; no immunocompromised patients.
  □ No difference in primary endpoint (hospitalisation within 28 d) between treatment group and placebo.

- Gharbharan et al. Clin Microbiol Infect 2022. Comparator study: plasma from non-convalescent patients in the control arm. Treatment within 7 days of symptom onset. Patients with at least one risk factor for progression to a severe form of the disease (in fact, mainly unvaccinated patients, 30% with pulmonary or cardiac disease). Minimum PC neutralising titre = 1/160
  □ No benefit demonstrated (although there was a trend towards greater improvement in clinical score in patients treated in the first 5 days). Trial stopped prematurely due to availability of monoclonal antibody treatments and the difficulty in obtaining plasmas from uninfected and unvaccinated individuals for the control group.

- Millat-Martinez P, et al. Nat Comm 2022. Meta-analysis of the 2 randomised therapeutic trials CoV-Early and COnV-ert which were pooled. Primary endpoint: time to resolution of symptoms and hospitalisation. 7% of participants seronegative at inclusion. No impact of PC.

A meta-analysis available in preprint (Levine AC, et al. medRxiv 2022) suggests a benefit in terms of reducing the risk of hospitalisation if treatment is administered within 5 days of the onset of symptoms and provided that the level of neutralising antibodies to PC is high. However, these results essentially reflect the findings of the Sullivan study, which involved a much larger group than the other studies (n=590/arm).

None of the studies included a highly immunocompromised population and the description of the PC used did not clearly indicate the neutralising antibody titres on the main variants of interest at the time of the intervention.

Furthermore, with regard to the use of PC at a later stage of the disease, the data in the literature show divergent results, but overall suggest that there is no clinical benefit in hospitalised patients, apart from a positive signal in patients treated because of persistent viral replication beyond the acute phase of the disease.

- Early discontinuation of the PCC arm in RECOVERY[1] (patients admitted to intensive care) for futility (RECOVERY Collaborative Group, Lancet 2021)

- Relative success in patients with persistent viral replication: benefit in patients with B lymphoid haemopathies (Hueso T, el al. Leukemia 2022)

- Reduced mortality (HR,0.52 ;95% CI, 0.29-0.92) in a retrospective cohort of patients with haematological malignancies who received PC compared with untreated patients, regardless of the time from symptom onset to intervention (Thompson MA, et al. JAMA Oncol 2021)

1 https://www.recoverytrial.net/news/statement-from-the-recovery-trial-chief-investigators-15-january-2021-recovery-trial-closes-recruitment-to-convalescent-plasma-treatment-for-patients-hospitalised-with-covid-19

Group opinion

Considering that :

- the available scientific evidence gives conflicting signals as to the efficacy of PC administered in the early phase of COVID-19 (although there is still some doubt as to the possible benefit of early administration of PC with a high neutralising antibody titre);

- the lack of assurance as to the availability, within a timeframe compatible with early administration, of batches of PC with a high neutralising antibody titre against the variants of interest circulating at time "t";

- the reduced neutralising activity of the batches of PC pre-selected and directly available on the majority variants in France at the beginning of 2023, which would mean administering very large volumes of plasma in order to obtain sufficient antiviral activity *in vivo;*

the AVATHER group does not recommend the use of PC for the early treatment of COVID-19, including in patients who are immunocompromised and/or at high risk of severe COVID-19. This opinion may be updated if new data become available.

However, the AVATHER Group accepts that**, as a last resort and in exceptional circumstances,** the use of PC as an early treatment may be discussed on an individual basis, when no other therapeutic option can be envisaged. In such cases, every effort should be made to ensure that the batch of PC used has significant neutralising activity against the variant in question in the patient concerned or, failing that, against the main variants currently circulating in France.

The use of sotrovimab (Xevudy®) in the current epidemic context for the treatment of COVID-19

The data available in the literature highlight :

- *In vitro* studies with whole virus: modest but real activity of sotrovimab on circulating SARS- CoV-2 strains, in particular BQ1, BQ1.1 and XBB.1 (Touret F, et al. BioRxiv 2022)

- It should be noted that when pseudoviruses or cell lines over-expressing ACE-2 are used, artificially low neutralising activity is measured, with the exception of a recent study in which sotrovimab was the only monoclonal antibody to retain *minimal* neutralising activity against XBB.1 (albeit reduced by a factor of 10 compared with the ancestral B.1 strain) (Arora P, et al. Lancet Infect Dis 2023). Neutralisation studies using plasma from patients who have received sotrovimab would be desirable to complement these *in vitro* studies.

- *In vivo* studies: a neutralising activity of sotrovimab has also been demonstrated (lower viral load in the lungs) in the hamster model (Driouich JS, et al. bioRxiv 2023) and in the K18/hACE-2 mouse model (Addetia A, et al. bioRxiv 2023).

- In addition, sotrovimab also retains its ability to bind to the BQ.1.1 and XBB.1 spike proteins, as well as its ability to induce antibody-dependent cell-mediated cytotoxicity (ADCC).

Real-life studies had also shown some efficacy of sotrovimab against circulating Omicron variants (Mazzota V, et al. J Med Virol. 2023), particularly BA.2, even though *in vitro* neutralising activity was greatly reduced (Bruel T, et al. Nat Med. 2022). The British real-life OpenSAFELY study concluded that sotrovimab and nirmatrelvir/ritonavir were equally effective in early treatment (Zheng B et al. MedRXiv 2023). However, these studies have methodological limitations.

Sotrovimab therefore remains the only available monoclonal antibody to retain some activity against the Omicron strains in circulation at the start of 2023, although this activity is much weaker than that of the first monoclonal antibodies against older viral strains.

Group opinion

Evidence of preclinical activity of sotrovimab on Omicron sub-variants in circulation in France at the start of 2023 remains limited and needs to be substantiated.
However, unlike the PC :

- There is *in vitro and in vivo* neutralisation data against circulating strains;
- the reproducibility of this activity in the treatment administered to the patient is guaranteed;
- the conditions of use and availability of the product are known and controlled.

The AVATHER Group therefore considers that, when it is totally impossible to use the first- and second-line therapeutic solutions of nirmatrelvir/ritonavir (Paxlovid®) and remdesivir (Veklury®), and only in this case, sotrovimab (Xevudy®) may be considered as a third-line treatment for immunocompromised patients at risk.

Summary by the AVATHER group on the therapeutic strategy in the early phase of COVID-19

The Group reaffirms its recommendation of 16 January 2023 and the MAbTher Group's previous recommendations on :

- Prioritisation of nirmatrelvir/ritonavir (Paxlovid®) as first-line treatment

- The use of remdesivir (Veklury®) as a second-line treatment when nirmatrelvir/ritonavir (Paxlovid®) cannot be used.

- The withdrawal of the monoclonal antibody combination tixagevimab+cilgavimab (Evusheld®) as a therapeutic option (curative and prophylactic) in the current epidemic context, due to the lack of activity of this combination against the majority variants at present.

The group also recommends :

- The use of sotrovimab (Xevudy®) as a third-line option in the early treatment of SARS CoV-2 infection in immunocompromised individuals at high risk of severe disease, if and only if the first- and second-line options are completely unavailable.

To date, the AVATHER group does not recommend the use of PC as an early treatment for COVID-19. This position may be updated if new data become available.

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