Convalescent plasma therapy in immunocompromised patients infected with the BA.1 or BA.2 Omicron SARS-CoV-2

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Abstract

The emergence of SARS-CoV-2 Omicron variant has led to a complete reconfiguration of the therapeutic landscape, with most monoclonal antibodies having lost any neutralization activity. We report here a case series of 75 immunocompromised patients infected by the Omicron variant who benefited of convalescent plasma. At baseline, 49 (68%) of the participants had a WHO score of 5 and 23 (32%) a WHO score of 6. At day 28 the case fatality was 24%. We observed no significant difference in the clinical outcome between patients with hematological malignancies, solid organ transplantation or auto-immune diseases. These promising results require controlled studies.

Introduction

Immunocompromised patients are at high risk of severe COVID-19. Since they might not elicit an adequate immune response after vaccination, passive immunization using ex-vivo produced neutralizing antibodies is one of the key therapeutic options in such populations[1]. Monoclonal anti-spike antibodies have shown a great risk reduction of hospitalization or death in immunocompetent patients[2,3]. However, emerging Omicron SARS-CoV-2 variants appeared to be completely or partially resistant to available monoclonal antibodies[4]. Early treatment with COVID-19 convalescent plasma (CCP) in unvaccinated immunocompetent patients has been shown to be associated with a lower risk of hospitalization[5]. Therefore, even if monoclonal antibodies seem associated with a greater risk reduction of disease progression than CCP, the polyclonal characteristics of CCP might be of particular interest in the context of emergence of new variants. Early in the pandemic, high titer CCP has shown some efficacy in B-cell depleted patients[6,7] but little is known on the efficacy of CCP in immunosuppressed patients infected by Omicron variant. Here, we report a case series of 75 immunocompromised patients infected by the BA.1 or BA.2 Omicron SARS-CoV-2 subvariants and treated

with high titer Omicron CCP.

Methods

We retrospectively analyzed the data from a nationwide, observational and multicentric study based on the French CCP Early Access Program. Between December 29th 2021 and March 16th 2022, 32 centers located in France requested the use of CCP during the SARS-CoV-2 Omicron variant wave. Due to underlying disease or treatment administered, patients with hematological malignancy (HM), solid organ transplanted recipients (SOTR) or those treated for autoimmune disease (AID) were considered immunosuppressed and eligible for CCP early access program. Infection with a B1 or BA.2 SARS-CoV-2 subvariants was documented on nasopharyngeal swab. We considered a threshold of positivity for anti-Spike antibodies of > 260 BAU/mL, as the ability of vaccines to prevent severe forms of COVID-19[8]. Every patient was informed of the study protocol and none refused to participate. Data was anonymized according to the French Law and ethical clearance was obtained from the French Infectious Diseases Society (CER-MIT 2022-0702).

We administered two consecutive transfusions of two ABO compatible high titers convalescent plasma units (200-220 mL each) at days 0 and 1. Transfused CCP were initially provided by pre-Omicron convalescent vaccinated donors with very high anti-spike IgG ratio (> 9, ELISA Euroimmun) to ensure anti-Omicron seroneutralization ability[9] and after mid-January 2022 by Omicron convalescent vaccinated donors with high-anti spike IgG ratio (> 6, ELISA Euroimmun). The primary outcome was the overall survival (OS) at day 28 after plasma infusion (d28).

Results

Among 249 requests for CCP during the study period, 225 (78%) were accepted and 81 (36%) had available follow-up until d28 at time of study analysis. Six patients were excluded because they finally did not receive any CCP despite a positive answer to CCP request (2 sotrovimab treatment, 1 intensive care physician's refusal, 2 spontaneous improvements, and 1 premature death). A total of 75 (33%) patients were analyzed **(Table 1)** . The most frequent underlying immunodeficiency was HM (69%) and most patients had received B-cell depletion therapy such as rituximab (68%). The remaining patients were SOTR (16%) or had AID (12%). Of note, 91% of the cohort was vaccinated with at least two doses. An anti SARS-CoV2 Spike protein antibodies > 260 BAU/mL was reported in 11% of patients, with a higher rate in SOTR (33%, *vs* 6% in HM and 11% in AID; p=0.03).

C-reactive protein decreased significantly between d0 and d7 after CCP infusion (101 (CI 79-124) *vs* 37 (CI 25-48) mg/L, $p< 0.0001$). At d7, 48 patients (64%) improved their conditions, 16 (21%) were discharged from hospital, 7 (10%) have been transferred to intensive care unit, and 6 (8%) had died. At day 28, the OS of whole cohort was 76% (CI = 65-84). The type of underlying immunosuppression did not impact OS (77% (95 % CI = 63-86) for HM, 82% (95 % CI = 45-95) for AID, and 71% (95 % CI = 88-40) for SOTR, p=0.84), whereas OS was higher in patient with WHO score 5 compared to WHO score 6 at the day of CCP infusion (88 % (95 % CI = 94-75) vs 53 % (95 % CI = 69-29), p =0.0009) **(Figure 1)** .

Discussion

We report herein an observational cohort of immunosuppressed patients, mostly with HM (almost all with B lymphoid disease), infected by the Omicron subvariants BA.1 or BA.2, and treated with CCP. The 28-days OS for the whole cohort was 76% (CI = 65-84) without differences according to the type of immunosuppression whereas the severity of COVID-19 at the time of CCP infusion greatly impacts the outcome. Indeed patients with high flow oxygen had a poor outcome despite CCP infusion with 53 % 28-days OS.

Early in the pandemic, our team reported the interest of CCP in B-depleted patients such as patients with CLL or treated with rituximab[11]. Despite the efficacy of CCP in such patients our results are quite disappointing. Indeed, in the recent observational study from the EPICOVIDEHA registry, mortality rate among hospitalized HM patients infected with Omicron was 16.5% that reaches 23% 30-day mortality in patients with chronic lymphoid leukemia (CLL)[10]. Is to note that in our cohort, 32 % of patients needed high flow oxygen at the time of CCP infusion that could explain the mitigate response after CCP infusion.

The beneficial effect of CCP was also described in patients with primary antibody deficiency with a clinical improvement and a decreasing of the viral load[12]. Concerning SOTR, few data are available with two relevant series of 10 and 13 patients reporting the feasibility of CCP with a mortality rate of 10 and 23% respectively linked to COVID-19[13,14].

To date, the time of CCP infusion remains debated. While B-depleted patients with high oxygen need and treated with CCP had a poor outcome[7], it could be interesting in similar patients with prolonged COVID-19[11]. Indeed, clinicians must distinguish patients with protracted disease as "smoldering COVID" from patients presenting with aggressive course. Besides the time between CCP infusion and the symptoms onset, the disease course should be informative and must be take into account in the decision to use CCP.

In a context of urgent need for therapeutic options when new SARS-CoV-2 variants emerge and escape current monoclonal antibodies, CCP remains an interesting treatment option for immunosuppressed patients whatever the underlying disease. Furthermore, some effort must be made to better anticipate disease course that should guide the timing of CCP infusion.

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Acquisition of data: BDVDM

Analysis and interpretation of data: QR, LP

Drafting of the manuscript: QR, BDVDM, KL

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QR, BDVDM, LP, YAA, LL declare they have no competing interest.

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Legend table 1: Baseline characteristics of the 75 immunocompromised patients infected with the BA.1 or BA.2 Omicron subvariants of SARS-CoV-2 and treated with CCP. CCP: COVD-19 convalescent plasma. BAU: Binding antibody unit, WHO score 5: Hospitalized, oxygen by mask or nasal prongs, WHO 6: Hospitalized, oxygen by non-invasive ventilation or high flow.

Legend figure 1: Overall survival of whole cohort (**A**) Overall survival according to underlying immunosuppression (**B**) and COVID-19 severity at the time of CCP infusion (**C**). AID: autoimmune disease; HM: hematological malignancy; SOTR: solid organ transplant recipient, WHO score 5: Hospitalized, oxygen by mask or nasal prongs, WHO 6: Hospitalized, oxygen by non-invasive ventilation or high flow.

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