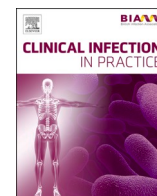




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## Case Reports and Series

## Efficacy of convalescent plasma therapy in immunocompromised patients with COVID-19: A case report

Genni Casarola<sup>a,b,1</sup>, Marco D'Abbondanza<sup>a,b,1</sup>, Rosa Curcio<sup>a,b</sup>, Riccardo Alcidi<sup>a,b</sup>, Tommaso Campanella<sup>a,b</sup>, Rachele Rossi<sup>a,b</sup>, Jessica Fusaro<sup>a,c</sup>, Vito Gandolfo<sup>a,b</sup>, Cinzia Di Giuli<sup>d</sup>, Chiara Laoreti<sup>a,c</sup>, Vito Veca<sup>a,b</sup>, Maria Comasia Leone<sup>a,b</sup>, Giacomo Pucci<sup>a,b,\*</sup>, Gaetano Vaudo<sup>a,b</sup>

<sup>a</sup> Department of Medicine and Surgery, University of Perugia, Perugia, Italy

<sup>b</sup> COVID-19 Unit, Terni University Hospital, Terni, Italy

<sup>c</sup> Unit of Internal Medicine, "S.Maria della Misericordia" University Hospital, Perugia

<sup>d</sup> Clinical Infectious Disease, Terni University Hospital, Terni, Italy

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## ABSTRACT

**Background:** Management of immunocompromised COVID-19 patients is the object of current debate. Accumulating evidence suggest that treatment with high-titer COVID-19 convalescent plasma (CCP) may be effective in this characteristic clinical scenario.

**Case report:** A 52-years old immunocompromised female patient, previously treated with rituximab for low grade B-cell lymphoma, showed prolonged SARS-CoV-2 shedding and a long-term course of signs of severe COVID-19. A first cycle of treatment with remdesivir, a nucleotide analogue prodrug effective in inhibiting SARS-CoV-2 replication, did not provide fully and sustained clinical remission. A second hospitalization was deemed necessary after 10 days from the first hospital discharge due to recrudescence of symptoms of severe COVID-19 and the evidence of bilateral interstitial pneumonia at the chest-CT scan. Clinical and radiological findings completely disappeared after CCP administration. The viral culture confirmed the absence of SARS-CoV-2-related cytopathic effect. The clinical evaluation, performed two months after hospital discharge, was unremarkable.

**Results:** Findings from our case report suggest that the host T-cell specific response to SARS-CoV-2 is not sufficient to reduce viral load in the absence of neutralizing antibodies. Acquired immune antibodies and/or related components passively infused with CCP might help in boosting the plasma recipient response to the virus and promoting complete viral clearance.

**Conclusions:** Independently from negative results in immunocompetent individuals, the potential effectiveness of CCP infusion in selected cohorts of patients with primary or secondary impaired immune response should be tested. Further research about mechanisms of host response in immunocompromised patients with SARS-CoV-2 infection is required.

## Case report

On November 5th, 2020, during a screening campaign, a 53-years old woman was found positive at the real-time polymerase chain reaction (RT-PCR) for SARS-CoV-2 RNA performed on the nasopharyngeal swab. She was asymptomatic for about 15 days. Subsequently, she progressively developed a cohort of symptoms like fever (up to 39.5 °C),

ageusia, anosmia, asthenia and dyspnea and was eventually hospitalized (December 7th, day 33). In her past medical history she had a low grade B-cell lymphoma diagnosed on November 2018 treated with a first-line therapy with bendamustine and rituximab from December 2018 to May 2019 and then with rituximab until August 2020 as maintenance treatment. At that time, a diagnosis of complete remission was made based on a FDG-PET/CT scan negative for recurrences and rituximab

\* Corresponding author at: Department of Medicine and Surgery, University of Perugia, Unit of Internal Medicine, Terni University Hospital, Piazzale Tristano di Joannuccio, 1, IT-05100 Terni, Italy.

E-mail address: [giacomo.pucci@unipg.it](mailto:giacomo.pucci@unipg.it) (G. Pucci).

<sup>1</sup> Joint first authors.

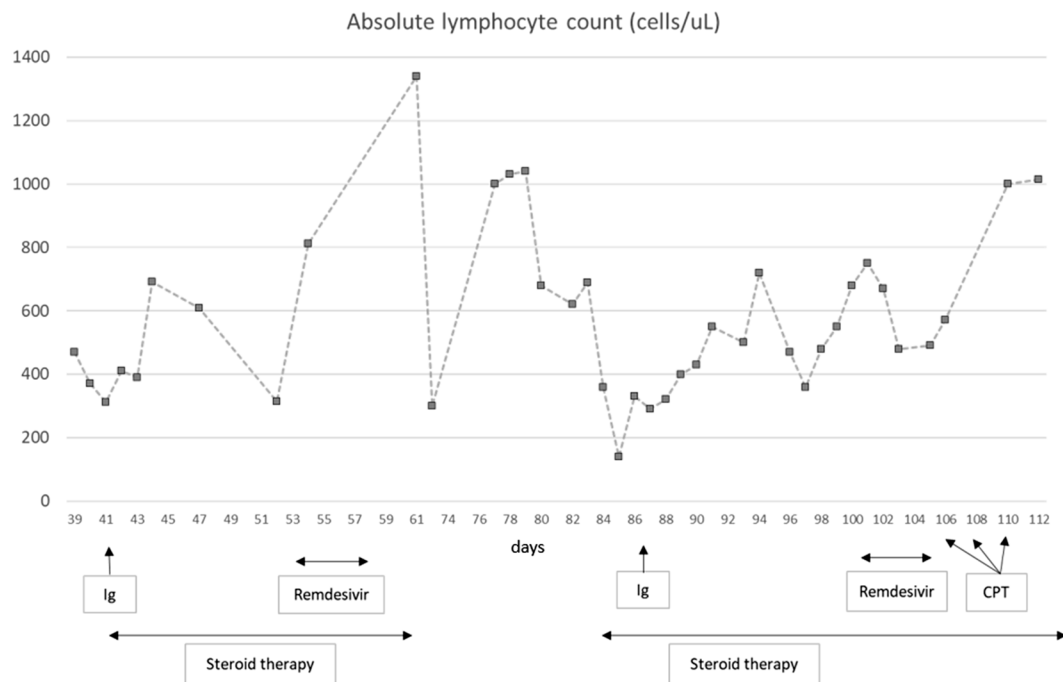
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**Fig. 1.** Absolute lymphocyte count and therapeutic strategies in a 58-years old female patient with severe COVID-19 and rituximab-associated sustained B-cell depletion. Ig = intravenous immunoglobulins, CPT: COVID-19 convalescent plasma.

was discontinued.

Upon hospitalization, a high-resolution chest CT scan showed bilateral interstitial pneumonia. Peripheral oxygen saturation was 92% while breathing ambient air; treatment with oxygen mask and intravenous dexamethasone were promptly initiated. Laboratory exams showed hypogammaglobulinemia and antibiotic prophylaxis plus immunoglobulin replacement were also administered. Serological testing for COVID-19 antibodies was negative for both IgM and IgG. Fever rose up again 3 days later (day 52) and was accompanied with recurrence of progressive dyspnea, respiratory failure and laboratory evidence of a reduction in the absolute lymphocyte count. The RT-PCR resulted positive at the nasopharyngeal swab (17<sup>o</sup> cycle of amplification). Spanish-originated SARS-CoV-2 variant A222V was identified at the genome sequencing. The viral culture showed the presence of viable virus. For this reason a cycle of treatment with remdesivir, a nucleotide analogue prodrug effective in inhibiting SARS-CoV-2 replication, was initiated for compassionate use (day 53) and was followed by partial clinical improvement and a resolution of symptoms. On day 74, after being discharged home afebrile and in relative good conditions (day 61), she was admitted to the emergency department for fever and worsening dyspnea. A chest CT scan confirmed the presence of interstitial pneumonia with bilateral areas of consolidation. A viral culture for SARS-CoV-2 was repeated on day 100 and confirmed virus viability through the evidence of cytopathic effect on cultured cells. The patient never recovered from respiratory failure and need for oxygen supplementation. A reduced absolute lymphocyte count was always present at the laboratory assessment. A second cycle of remdesivir was not followed by any clinically detectable improvement. Therefore, three infusions of high-titer COVID-19 convalescent plasma (CCP, 1:320, 1:160, 1:80 respectively, on day 105, 107 and 109) from donors previously infected with SARS-CoV-2, were administered on top of concurrent treatment. On the following days, the patient experienced a rapid improvement of respiratory function: absolute lymphocyte count rapidly increased, oxygen supplementation was down-titrated and stopped afterwards. Fever disappeared and COVID-related indexes of systemic inflammation progressively decreased. On day 114, after more than three months from its detection, the nasopharyngeal specimen was negative for SARS-CoV-2

and the viral culture confirmed the absence of SARS-CoV-2-related cytopathic effect. The patient was discharged home in good conditions. The clinical evaluation at the follow-up visit performed two months after discharge was unremarkable.

Protracted SARS-CoV-2 infection is often seen in immunocompromised patients. Shedding of viable virus was found up to 105 days after initial positive test and was associated with prolonged infectiveness, duration and severity of COVID-19 (Tarhini et al., 2021). Persistent infection of SARS-CoV-2 in immunocompromised patients was also shown to induce an accelerated viral evolution that, in turn, could favor the emergence of *in vivo* novel viral variants (Choi et al., 2020). Rituximab, an anti-CD20 monoclonal antibody determining a sustained B-cell depletion and secondary impairment of humoral immunity, has been identified as a risk factor for adverse outcomes in patients infected by SARS-CoV-2. B-cell depletion impairs antiviral immunity over the long term, favors the development of protracted forms of COVID-19 and related chronic complications, increases the risk of reinfection and potentially weakens vaccine efficacy in non-infected people (Yasuda et al., 2020).

Case series reports demonstrated that in patients with acquired immune deficiencies of various etiologies (including treatment with rituximab) and affected by severe COVID-19, treatment with CCP was often accompanied by a clinical improvement in a very high proportion of patients, going from 86% to 94% (Delgado-Fernández et al., 2021; Hueso et al., 2020; Rodionov et al., 2021). Of relevance, the efficacy of treatment was independent from duration of disease. Indeed, favorable outcomes were observed even in patients with prolonged SARS-CoV-2 infection lasting more than 88 days (Delgado-Fernández et al., 2021).

In our case, treatment with CCP demonstrated to be effective even if administered after 105 days from the first detection of SARS-CoV-2 RNA. This finding is in clear contrast with results of initial trials exploring the effectiveness of treatment with CCP in immunocompetent individuals with COVID-19, where no overt benefits were observed either if CCP was administered on top of current treatment during the acute phase of the disease in hospitalized patients, as demonstrated in the RECOVERY trial (RECOVERY Collaborative Group, 2021), or as early treatment option in non-hospitalized subjects with mild symptoms (Korley et al., 2021).

In the described case, the potential contribution of CCP in the eventual recovery could not be entirely disentangled from that provided by corticosteroids and remdesivir co-administration. However, when administered in the initial phase of the disease, such drugs showed limited efficacy in promoting complete viral clearance and normalization of lymphocyte count over the long term (Fig. 1). Given the absence of serial viral genome sequencing, it cannot also be excluded that SARS-CoV-2 novel *in vivo* mutations, reinfection or superinfection may have caused, in this specific case, a recrudescence of symptoms. Indeed, as previously said, an impaired CD20-related B-cell function induced by rituximab is a known risk factor of each of these conditions (Tarhini et al., 2021 May 20).

On a more general perspective, findings from our case report suggest that the host T-cell specific response to SARS-CoV-2 is not sufficient to reduce viral load in the absence of neutralizing antibodies. Acquired immune antibodies and/or related components passively infused with CCP, such as, for instance, exosomes, might have a key role in boosting the plasma recipient response to the virus and promoting complete viral clearance (Askenase, 2020). Currently, high-titer CCP is not recommended in the treatment guidelines of severe COVID-19 immunocompetent patients due to its futility, as it was recently observed in randomized clinical trials (RECOVERY Collaborative Group, 2021; Korley et al., 2021; COVID-19 Treatment Guidelines Panel, 2019). Conversely, a clear indication in favor or against treatment with CCP in patients with impaired immunity has not been released to date and the efficacy and safety of such treatment remains to be tested in highly selected cases. We believe that evidence from previous literature and our clinical case report should stimulate further research about mechanisms of host response in immunocompromised patients with SARS-CoV-2 infection and the potential role of CCP infusion. On a same degree, independently from negative results in immunocompetent individuals, clinical trials addressing the issue of effectiveness and safety of high-titer CCP in selected cohorts of patients with primary or secondary impaired immune response are urgently needed.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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