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# Convalescent plasma for persisting COVID-19 following therapeutic lymphocyte depletion: a report of rapid recovery

We read with deep interest the report by Tepasse *et al.*[1] concerning two cases of persisting viraemia in coronavirus disease 2019 (COVID-19) with fatal outcome. Whilst severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in the early stages of infection has been well described, less is known about the development of antibodies to SARS-CoV-2, clearance of RNA shedding and clinical outcome of COVID-19. In addition, the impact of immunosuppressive treatments on disease severity is not yet established, but several reports suggest a more prolonged disease in patients under rituximab, a B-cell depleting drug.[2–4] Here we report a case of persisting COVID-19, following combined treatment with rituximab and bendamustine for lymphoma, which immediately recovered after convalescent plasma transfusion. We think that this case raises promising perspectives for immunocompromised patients with persisting COVID-19.

A 76-year-old woman was diagnosed in 2019 with orbital and meningeal marginal zone lymphoma in the context of probable unrecognised Sjögren's syndrome with positive salivary gland biopsy (focus score = 2). Bendamustine and rituximab were administrated on 12 February (70 mg/m$^2$ of bendamustine) and 16 March 2020 (90 mg/m$^2$), inducing a decay of lymphocyte count from 1410/µl on 11 February to 160/µl on 17 March 2020. Granulocyte-colony stimulating factor prophylaxis was started thereafter.

She consulted her general practitioner on 26 March 2020 (Day 1) with fever, diarrhoea and deep fatigue. Home surveillance was initially decided. On 1 April (Day 7), she was referred to our hospital for severe pneumonia (tachypnoea, fever and desaturation requiring oxygen). Blood testing revealed lymphopenia (550/µl) in all lymphocytic subtypes: 88 lymphocyte T CD4 cells/µl (16·0%), 385 lymphocyte T CD8 cells/µl (69·6%), 3 lymphocyte B cells/µl (0·6%), 59 natural killer cells/µl (10·7%), associated with thrombocytopenia (65 × 10$^9$/l) and an inflammatory syndrome [neutrophilic leucocytosis of 25·11 × 10$^3$/µl and a C-reactive protein (CRP) of 24 mg/l]. Ground-glass bilateral opacities and consolidations were observed on chest computed tomography (CT). SARS-CoV-2 infection was confirmed by RNA reverse transcriptase-polymerase chain reaction (RT-PCR) on a nasopharyngeal swab.

A combination of lopinavir/ritonavir was given between days 9 and 24. Faced with worsening of clinical symptoms (confusion and increased oxygen requirement) and extension of the opacities on chest CT, a treatment with prednisone (50 mg/day) for 7 days was introduced on day 27. Apyrexia and oxygen withdrawal ensued. However, symptoms relapsed within 48 h of prednisone withdrawal, and persisted during the sixth week of admission, requiring oxygen administration due to desaturation, relapse of fever.

Follow-up chest CT on day 36 and day 44 showed an increase in ground-glass and consolidation opacities. SARS-CoV-2 RNA remained positive on 10 repeated nasopharyngeal swab tests (Fig 1). By contrast, SARS-CoV-2 antibodies remained undetectable at Day 47. Intravenous convalescent plasma obtained from SARS-CoV-2 survivors was administered starting at day 50 over 2 days, after obtaining the patient's informed consent, (2 units of 200 ml/day). No adverse events occurred. The patient tested positive for SARS-CoV-2 anti-nucleocapsid and anti-Spike immunoglobulin G (IgG) after the two first plasma units. Her health condition quickly improved, allowing definitively withdrawing oxygen, apyrexia ensued, and a decrease in CRP level within 24 h was objectified. SARS-CoV-2 RNA became undetectable on Day 57 and remained negative on Day 62. She returned home on Day 69 and completely recovered after 17 additional days of follow-up.

## Discussion

To date, treatment of COVID-19 is still challenging and there is no specific recommended therapy. Despite the sequential introduction of different treatments, our patient experienced an unusual delayed clinical worsening, a persisting clinical infection and a prolonged viral shedding. Such a course is unusual, as the median time to clinical worsening is approximately 8–10 days. Furthermore, the median time until viral RNA clearance attested by PCR on a nasopharyngeal swab, is estimated around 17–24 days in hospitalised patients.[5] Prolonged viral RNA shedding over 15 days is not infrequent, especially in elderly and severe COVID-19 cases.[6] In patients with prolonged viral shedding, the symptoms had retrieved whilst SARS-COV-2 RNA remained detectable in pharyngeal swabs at

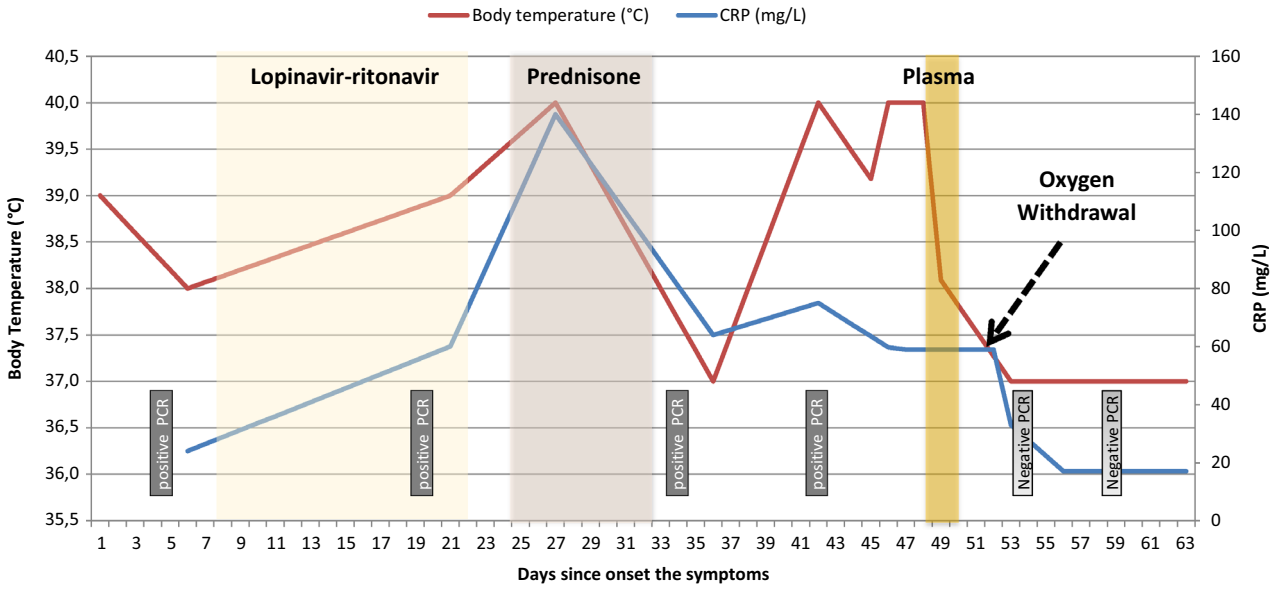


**Fig 1.** COVID-19 clinical course of the patient following combined treatment with rituximab and bendamustine for lymphoma.

day 54. Furthermore, in our patient, persistent pneumonia, abnormalities in the CT scan, and the levels of PCR cycle threshold values suggested a persisting viral replication and possible infectiousness. Seroconversion occurs after 7 days in 50% of patients and IgG are detected in >90% of patients after day 14.[7] High viral loads are reported during the first week of COVID-19, when viral isolation of SARS-CoV-2 is possible.

In the present case, spontaneous seroconversion never occurred, suggesting that the combination of bendamustine and rituximab induced an impairment of humoral and cellular response against SARS-CoV-2 due to persisting depletion of circulating $CD4^+$ T and B cells. Indeed, bendamustine preferentially inhibits $CD4^+$ lymphocytes,[8] while rituximab deeply depletes humoral and B-cell responses to infections.[9] Despite its reputation for good tolerance, rituximab may even induce severe life-threatening infections.[10] Although rituximab does not directly affect $CD20^-$ plasma cells producing antibodies, the antibody production can be impaired, as well as the antibody response after vaccination. Other B-cell functions may be altered by rituximab, notably the antigen presentation and cellular interactions with T cells and monocytes/macrophages through interleukin 6 production.[4] Thus, B-cell depleting drugs may delay the inflammatory response in COVID-19, which is tragically illustrated by a cytokine storm in the most severe cases, as illustrated by those reported by Tepasse *et al.*[1] We think that hyperimmune plasma from convalescent patients could provide a valuable input against SARS-CoV-2 infection in patients' immunosuppressed with rituximab.

In the present case, the rapid clinical improvement followed by viral clearance after administration of hyperimmune plasma argue that passively transferred antibodies played a key role in COVID-19 recovery. Convalescent plasma extracted from patients recovering from diverse infections contains neutralising antibodies against specific agents, and its efficacy has been diversely evaluated in patients with severe and acute COVID-19 infection.[11] In the present case, the transfusion was well tolerated and no transfusion-related acute lung injury was observed.[12]

To the best of our knowledge, we describe the first case of favourable outcome following convalescent plasma transfusion, in an immunocompromised patient with persisting COVID-19. Administration of neutralising antibodies may be a possible therapeutic approach in patients with persisting COVID-19 symptomatology in the context of deep immunosuppression.

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## Conflict of interest

The authors declare no competing financial interests.

## Author contribution

Evangéline Clark, Ionut L. Filip and Philippe Guilpain designed and wrote the paper. Edouard Tuaillon extracted virology data. All the authors revised the paper.

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