HemaSphere
Powered by EHA

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Case Report
OPEN ACCESS

Efficacy of Serotherapy on an N501Y Variant of SARS-CoV-2 in a Patient With Chronic Lymphocytic Leukemia

Colin Vercueil[1], Lauriane Eberst[1], Catherine Humbrecht[2], Luc-Matthieu Fornecker[3]

Correspondence: Colin Vercueil (colinvercueil@gmail.com).

We report the case of a 67-year-old man with chronic lymphocytic leukemia (CLL) (stage Binet A) diagnosed in 2017. At diagnosis, the patient had no enlarged lymph node, liver, or spleen, an isolated hyperlymphocytosis (lymphocytes = 11.66 x 10^9/L) with no anemia nor thrombocytopenia. Rai stage was zero (low risk). The previous follow-up consultation, 3 months before the event, had revealed a slow increase in lymphocytosis (21.0 10^9/L) but without cytopenia or peripheral tumor syndrome. At this time, the patient had no hypogammaglobulinemia (gammaglobulin = 8.8 g/L with IgG = 11.18 g/L). Watch and wait strategy was recommended. He had no other significant medical history and had not been vaccinated against coronavirus disease 2019 (COVID-19).

Polymerase chain reaction (PCR) testing for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was performed on a nasopharyngeal swab on March 29, 2021 (day 1), following contact with a confirmed case. At the time of the event, the patient presented with hyperleucocytosis at 19 10^9/L (lymphocytes = 15 10^9/L), normal hemoglobin level (150 g/L), and normal platelet count (182 10^9/L). This detected SARS-CoV-2 N501Y, the South African or Brazilian variant. Six days later, he reported cough, fatigue, and fever. Hypoxia developed on day 11 requiring hospitalization in the intensive care unit. The C-reactive protein (CRP) was 218.6 mg/L (Figure 1A). A thoracic computed tomography (CT) scan showed typical COVID-19 lesions with up to 50% pulmonary involvement (Figure 1B). Standard treatment was initiated at the day of hospitalization, including oxygen at 2 L/min, dexamethasone 6 mg daily, and enoxaparine at 4000 UI twice a day.

On day 15, his respiratory condition deteriorated, and diarrhea appeared. The infectious screening remained negative for bacterial and fungal infections.

Following a multidisciplinary board, convalescent plasma (CP) infusion was deemed the most appropriate treatment. The patient received a total volume of 845 mL (2 CP units) of fresh frozen plasma (FFP) on days 17 and 18. He did not receive intravenous immunoglobulin. His blood type was O RhD positive. Serology performed on day 17, before administration of CP, showed weak positivity for antibodies (IgG = 90.1 AU/mL).

By day 21, his general condition and respiratory parameters improved, along with the CRP. Oxygen was discontinued by day 24 and the patient was subsequently discharged the same day.

Follow-up after hospitalization showed a favorable clinical course. Nasopharyngeal swab became negative on day 31. Control chest CT 4 months after the episode showed partial regression of post–COVID-19 pulmonary lesions, involving 30% of the parenchyma.

As clinical characteristics of CLL and risk factors for severe COVID-19 overlap (advanced age, immunodeficiency), patients with CLL are at high risk of death.[1] So far, no specific treatments have emerged for these patients, and guidelines recommend best supportive care, regardless of the underlying hematologic disease.

CLL is associated with a dysfunctional innate and adaptive immune system. Hypogammaglobulinemia is often present at early stages and involves all immunoglobulin classes (IgG, IgM, IgA), which is directly correlated with infection risk.[2] Antibody responses to primary and secondary antigen-challenge are often inefficient and explain why vaccination failures are more frequent in these patients.[3] Functional defects in normal B-cells, T-cells, neutrophil, and natural killer are also described.[4] Reduced levels of several complement proteins are observed (40% of patients have reduced C1-C4 components), which is also associated with an increased susceptibility for infections.[5] Ye et al[6] reported the case of a COVID-19 infection in a newly diagnosed CLL patient. Despite positive serology (IgM and IgG SARS-CoV-2–specific antibodies), she developed severe pneumonia and was unable to effectively clear the virus after 69 days of follow-up.[6] Our patient developed a severe pneumonia despite a seroconversion with detection of specific anti–SARS-CoV-2 IgG.

Studies have shown that CP administration is an effective treatment against emerging pathogens such as SARS-CoV-2, with several underlying mechanisms. First, SARS-CoV-2 antibodies (IgG, IgM) from the donor directed against Spike1-receptor binding protein, Spike1-N-terminal domain, and Spike2 lead to limited viral amplification. Infusion of plasma from convalescent donors also provides immunomodulatory effects via anti-inflammatory cytokines (interleukin [IL]-4, IL-10, IL-13) that block the complement cascade, as well as inflammatory cytokines (IL-1β, IL-6, tumor necrosis factor-α) and autoantibodies that activate immune response. Finally, CP constitutes

[1]Oncology Department, Institut de Cancérologie Strasbourg Europe, France
[2]Etablissement Français du Sang, Strasbourg, France
[3]Hematology Department, Institut de Cancérologie Strasbourg Europe, France

HemaSphere (2021) 5:12(e655).
http://dx.doi.org/10.1097/HS9.0000000000000655.
Received: 9 June 2021 / Accepted: 27 September 2021

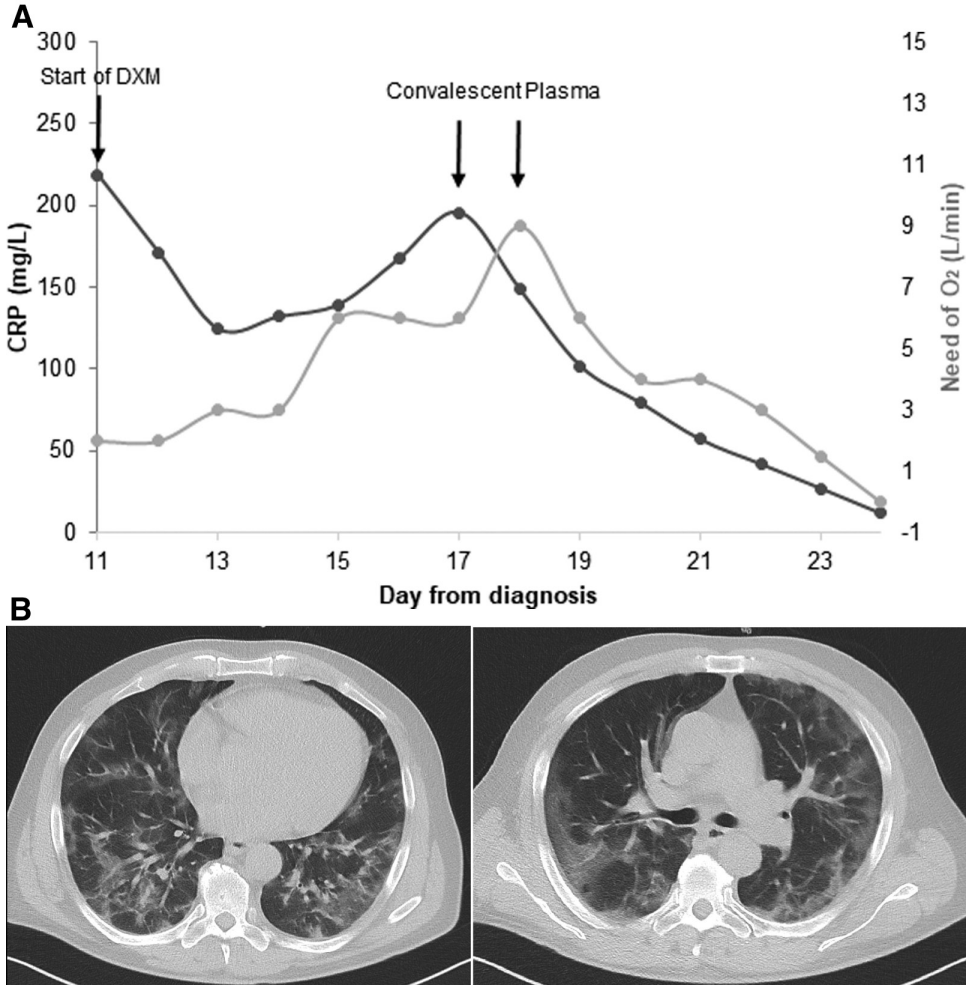

Figure 1. Paraclinical parameters of the patient during the acute phase. (A) Variations of paraclinical parameters during hospitalization. (B) Thoracic CT scan of the patient at day 11. Parenchymal invasion was assessed at 50%. CRP = C-reactive protein; CT = computed tomography; DXM = dexamethasone.

a refill in complement proteins such as C1-C4.[7] To our knowledge, effectiveness of CP infusion from a "wild type" donor on mutated forms of SARS-CoV-2 has not been described.

A recent case report showed that the 501Y.V2 SARS-CoV-2 variant can be responsible for severe reinfections after a first mild infection with "wild type" SARS-CoV-2.[8] Assessing cross immunity against emerging variants appears to be a main challenge to monitoring serotherapy and vaccine effectiveness.

The compassionate therapeutic use of CP outside clinical trials for the treatment of COVID-19 has been available in France since May 2020. Plasma donors for serotherapy are selected according to the following criteria: a history of symptomatic infection with SARS-CoV-2 with a positive reverse transcriptase-PCR, and clinical recovery, defined as the absence of symptoms for more than 28 days. After sampling, plasma serology is assessed (EUROIMMUN kit, Lübeck, Germany) and until July 2020, the FFP was qualified as "convalescent plasma" if the IgG ratio is above 5.7. This threshold has been shown to correlate with high titers of neutralizing antibodies.[9] The U.S. Food and Drug Administration (FDA) has retained a cut-off of 3.5 for the authorization of emergency use in the treatment of US patients.[10] The French blood bank has no information about any identification of SARS-CoV-2 mutants in its database. However, we traced the period of donation and the region of collection of the 4 FFP units used in our patient. Plasma had been harvested between the 5th and 6th of May 2020 and donors were all residents of Alsace in the Grand-Est region of France. The first case of infection with SARS-CoV-2 501Y.V2 in France was identified on December 31, 2020. We can therefore infer that the FFP received by our patient came from donors not infected by this specific mutant.

The SARS-CoV-2 mutations that were screened in our patient were Spike 501Y (commonly reported for the English, South African, and Brazilian variants), which was present, and Spike Del70 (specific of the English variant), which was absent.

A "flash" epidemiological survey conducted by the French Health Ministry showed an 18.0% incidence rate of the South African variant in mid-March 2021 in the Grand-Est region, compared with 0% for the Brazilian variant. It is therefore highly likely that the patient was a carrier of South African variant.

Published data on the efficacy of CP are contradictory. A meta-analysis showed a reduction of mortality for patients treated with CP,[11] but the plasma arm of the large randomized Randomised Evaluation of COVID-19 thERapY (RECOVERY) trial failed to confirm this trend.[9] The RECOVERY serology cut-off chosen for CP qualification was 6 (instead of 5.7 in France before July 2020), but patients received only 2 FFP bags instead of 4 in France. This study did not perform a subgroup analysis on patients with B-cell lymphoproliferative disorders such as CLL.

Our case illustrates the potential efficacy of the administration of plasma from "wild-type" COVID convalescent donors in CLL patients infected by the N501Y variant. There is certainly a need to further assess the place of CP in immunocompromised patients unable to produce a suitable humoral response after SARS-CoV-2 infection.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Scarfò L, Chatzikonstantinou T, Rigolin GM, et al. COVID-19 severity and mortality in patients with chronic lymphocytic leukemia: a joint study by ERIC, the European Research Initiative on CLL, and CLL Campus. *Leukemia.* 2020;34:2354–2363.
2. Morrison VA. Infectious complications of chronic lymphocytic leukaemia: pathogenesis, spectrum of infection, preventive approaches. *Best Pract Res Clin Haematol.* 2010;23:145–153.
3. Sinisalo M, Aittoniemi J, Käyhty H, et al. Vaccination against infections in chronic lymphocytic leukemia. *Leuk Lymphoma.* 2003;44:649–652.
4. Forconi F, Moss P. Perturbation of the normal immune system in patients with CLL. *Blood.* 2015;126:573–581.
5. Füst G, Miszlay Z, Czink E, et al. C1 and C4 abnormalities in chronic lymphocytic leukaemia and their significance. *Immunol Lett.* 1987;14:255–259.
6. Ye X, Xiao X, Li B, et al. Low humoral immune response and ineffective clearance of SARS-Cov-2 in a COVID-19 patient with CLL during a 69-day follow-up. *Front Oncol.* 2020;10:1272.
7. Rojas M, Rodríguez Y, Monsalve DM, et al. Convalescent plasma in COVID-19: possible mechanisms of action. *Autoimmun Rev.* 2020;19:102554.
8. Zucman N, Uhel F, Descamps D, et al. Severe reinfection with South African SARS-CoV-2 variant 501Y.V2: a case report. *Clin Infect Dis.* 2021 February 10. [Epub ahead of print].
9. RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. *Lancet.* 2021;397:2049–2059.
10. US Department of Health and Human Services Food and Drug Administration. Letter of authorization, reissuance of convalescent plasma EUA. Available at: https://www.fda.gov/media/141477/download. Accessed April 27, 2021.
11. Klassen SA, Senefeld JW, Johnson PW, et al. The effect of convalescent plasma therapy on mortality among patients with COVID-19: systematic review and meta-analysis. *Mayo Clin Proc.* 2021;96:1262–1275.