

Convalescent plasma and remdesivir for protracted COVID-19 in a patient with chronic lymphocytic leukaemia: a case report of late relapse after rapid initial response

Patients with chronic lymphocytic leukaemia (CLL) are at a particularly high risk of death related to coronavirus disease 2019 (COVID-19). A multinational cohort study reported a case-fatality rate of 37% in patients with CLL who were admitted to the hospital for COVID-19 between February and April 2020 irrespective of former therapies.¹ Considering the impaired humoral immune response of patients with CLL, it is hypothesised that administration of convalescent plasma may improve outcomes.² However, patients with haematological malignancies have been under represented in randomised controlled trials evaluating the safety and efficacy of convalescent plasma in COVID-19.^{3–5}

In the present study, we describe the case of a patient with CLL and protracted severe COVID-19 who achieved a rapid but not sustained clinical response to combined therapy with remdesivir and convalescent plasma. The patient provided written informed consent to report his case and verbal informed consent to receive experimental therapy with convalescent plasma. Further information about the collection and preparation of plasma as well as methods on performed whole-genome sequencing, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) reverse-transcriptase polymerase chain reaction (RT-PCR) and antibody tests, and viral culture are provided in the Data S1.

A 61-year-old male patient was diagnosed with CLL in 2019 [Binet B, modified Rai intermediate, immunoglobulin heavy-chain variable-region (*IGHV*) unmutated, no 17p deletion or tumour protein p53 (*TP53*) mutation]. He responded well to six cycles of fludarabine, cyclophosphamide and rituximab from February until July 2020 with clinical remission of enlarged lymph nodes to normal size, normalisation of haemoglobin and neutrophil counts, clearance of high lymphocyte count and undetectable minimal residual disease ($<10^{-4}$) by flow cytometry from peripheral blood. Immunoglobulin G (IgG) levels dropped from the lower normal range (7.8 g/l in June 2019, normal range: 7–16 g/l) before treatment to <5 g/l during treatment (4.6 g/l in June 2020). His medical history included cancer-associated pulmonary embolism in 2019, hypertension and prediabetes. Regular medication consisted of therapeutic-intensity apixaban, ramipril, and prophylactic therapy with trimethoprim-sulfamethoxazole and valaciclovir.

On 15 September 2020, the patient presented to his general practitioner with fever, nausea, loss of taste, dry cough

and myalgia. A RT-PCR of a nasopharyngeal swab was positive for SARS-CoV-2. The patient remained isolated at home until he was admitted to hospital 21 days after COVID-19 diagnosis for a deteriorating general state and a weight loss of 14 kg. On admission, the patient was febrile (38.8°C), but haemodynamically stable with sufficient peripheral oxygen saturation (Fig 1). The laboratory findings demonstrated elevated C-reactive protein (CRP; 17 mg/l, normal range: <5 mg/l), procalcitonin (0.20 µg/l, normal range: <0.1 µg/l), severe lymphocytopenia (0.14 g/l, normal range: 1.10–3.50 g/l) and low IgG level (3.8 g/l in October 2020). A chest X-ray showed opacities of the right lower lung lobe. The patient received a 5-day course of ceftriaxone for presumed bacterial superinfection of a COVID-19 pneumonia. Blood cultures showed no growth and the urine antigens for *Legionella pneumophila* and *Streptococcus pneumoniae* were negative.

On hospitalisation day 3 (i.e. 24 days after the diagnosis of COVID-19), the patient's oxygen saturation deteriorated (arterial partial pressure of oxygen of 65 mmHg under ambient air). Treatment with dexamethasone 6 mg daily and supplemental oxygen was initiated. Computed tomography showed extensive bilateral opacities without pulmonary embolism. At 31 days after diagnosis of COVID-19, the patient received intravenous remdesivir (loading dose of 200 mg followed by 4 days of 100 mg daily), and transfusion of 2 u of 200 ml convalescent plasma. Within 1 day after administration of remdesivir and convalescent plasma, the patient reported complete resolution of symptoms and was discharged. Prior to administration of remdesivir and convalescent plasma, RT-PCR and viral culture of a nasopharyngeal swab were both positive and serology showed absent SARS-CoV-2 anti-spike IgG antibodies. Repeat testing 4 days after completion of treatment showed negative viral culture and positive SARS-CoV-2 anti-spike IgG antibodies.

On 11 February 2021, the patient was readmitted for myalgia, cough, fever, diarrhoea, and nausea. He presented elevated CRP (82 mg/l), procalcitonin (0.88 µg/l), lymphopenia (0.74 g/l), and opacities in the right lower lung lobe on the chest X-ray. The IgG level on 13 January 2021 was 5.0 g/l. The SARS-CoV-2 RT-PCR and viral culture of a nasopharyngeal swab were positive, and comparison of the viral genome sequences between the first and second hospitalisation showed seven substitutions, indicating infection with the same virus strain (lineage B.1.160 by Pangolin, Data S1). The

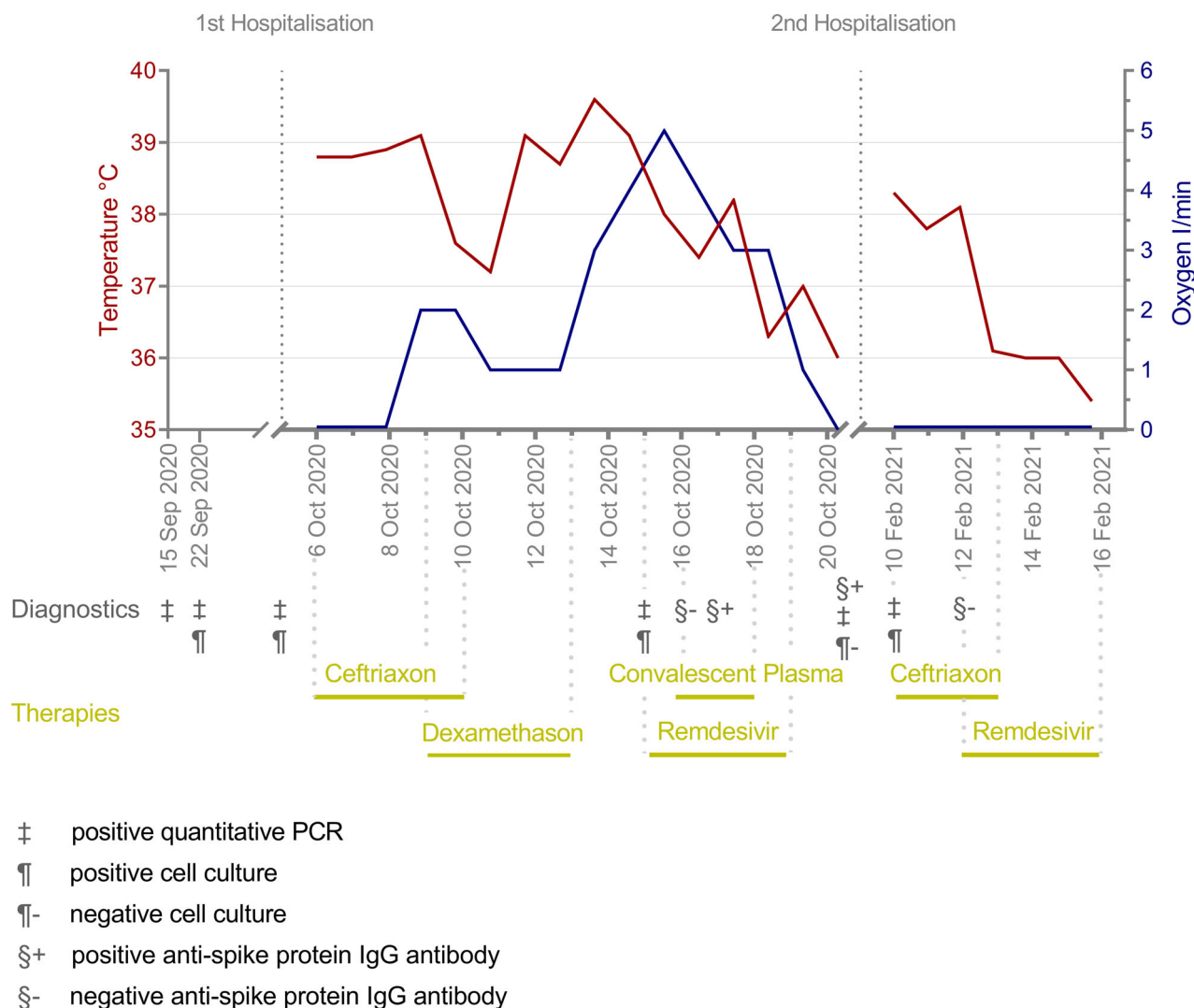


Fig 1. Hospitalisation records of oxygen therapy, temperature, diagnostic procedures and therapies. IgG, immunoglobulin G; PCR, polymerase chain reaction.

serology showed absent SARS-CoV-2 anti-spike IgG antibodies. Whilst receiving ceftriaxone for 3 days and remdesivir for 5 days, the patient presented with complete resolution of symptoms. Given the lower disease severity compared to the initial admission, convalescent plasma was not administered.

In summary, this patient presented a protracted course of COVID-19 characterised by several weeks of viral syndrome, weight loss, and persistent viral replication. After receiving a combination of remdesivir and convalescent plasma, rapid and complete symptom resolution was achieved until 3-5 months after discharge, when a second episode of COVID-19 with the same virus strain was diagnosed. Seven nucleotide substitutions between the two SARS-CoV-2 genome sequences were detected, which is consistent with the estimated expected evolution of the virus.⁶ It is therefore likely that the patient had incomplete viral clearance despite treatment and relapsed after loss of antibodies, although, a re-infection with the same virus strain cannot be excluded. Prolonged viral shedding has been

reported in patients with haematological disorders receiving chemo- or immunotherapy,⁷ which supports the hypothesis that viral clearance in patients with an impaired immune system can take several weeks.

A previous case report indicates that in immunocompromised patients with COVID-19, inflammation and symptoms improve on remdesivir, but recur upon cessation of treatment.⁸ These findings suggest that ongoing viral replication contributes to protracted disease manifestations, but also that suppression of viral replication alone may not be sufficient to achieve a sustained disease control in immunocompromised patients. Convalescent plasma or monoclonal antibodies may improve outcomes in such patients with inability to produce neutralising antibodies, as indicated by previous case reports,^{2,9} and the recent results from the RECOVERY trial (ClinicalTrials.gov Identifier: NCT04381936), in which monoclonal antibodies improved 28-day mortality in seronegative but not seropositive patients.¹⁰

We report the case of an immunocompromised seronegative patient with protracted COVID-19, who received remdesivir and convalescent plasma and subsequently presented rapid clinical improvement with reduced viral replication, although not viral clearance, and a late relapse. This case highlights that long-term follow-up of such patients is important because combined therapy with remdesivir and convalescent plasma may not lead to immunity or complete viral elimination.

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Author contributions

Carla Schenker and Tobias Tritschler wrote the paper. All authors were involved in the patient's care, critically revised the manuscript and approved the final version.

Conflict of interest

The authors declare no competing financial interest.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supplementary Methods.

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