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Treatment of SARS-CoV-2 relapse with remdesivir and neutralizing antibodies cocktail in a patient with X-linked agammaglobulinaemia

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ABSTRACT

During the coronavirus disease 2019 (COVID-19) pandemic, patients with humoral immunodeficiency are at higher risk of developing chronic infection and having a negative outcome. Few data are available on therapeutic options for this population. This case report discusses the treatment of disease relapse with remdesivir and monoclonal antibodies in an adult patient with X-linked agammaglobulinaemia.

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Case presentation

Patients with coronavirus disease 2019 (COVID-19) affected by immunodeficiencies can develop severe manifestations of the infection and are at higher risk of recurrence, with recovery of replication-competent virus reported beyond 20 days, and as long as 143 days after a positive severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) test result ([Centers for Disease Control and Prevention, 2021](#)).

X-linked agammaglobulinaemia (XLA) is a primary humoral immunodeficiency that causes a significant reduction in mature B-cell count and serum immunoglobulin, and lack of recall humoral response to antigens.

This case report describes the clinical course of a 28-year-old patient with a history of XLA who was re-admitted to hospital

with fever, asthenia and diarrhoea after recent hospitalization for SARS-CoV-2 pneumonia. His past medical history revealed multiple episodes of upper and lower respiratory tract infections before the delayed diagnosis that caused bronchiectasis. Since the diagnosis of XLA, at 6 years of age, he had been on replacement immunoglobulin therapy with 500 mg/kg/4 weeks intravenous immunoglobulin (IVIG).

During his previous hospital stay, the patient needed low flow oxygen therapy, and received remdesivir (5-day course), dexamethasone 6 mg (10-day course), empirical antibiotic therapy with amikacin (10-day course) and cefotaxime (14-day course), and a further dose of IVIG 20 g. He was discharged from hospital after testing negative for SARS-CoV-2 RNA by reverse transcription polymerase chain reaction (RT-PCR) using nasopharyngeal swab, 11 days after the first positive test.

Two weeks after hospital discharge, the patient suffered a relapse of high recurrent fever associated with diarrhoea, and was admitted to a COVID-19-free ward after testing negative for SARS-CoV-2 RNA RT-PCR using nasopharyngeal swab. He denied shortness of breath and chest tightness, but he was persistently

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febrile despite starting empirical antibiotic therapy with ceftriaxone 2 g every 24 h. Antibiotic therapy was stopped on day 14 post admission. Blood tests showed elevated C-reactive protein (CRP) (6.72 mg/dL), serum IL-6 (33.5 ng/L) and serum ferritin (1425 µg/L); mild hypertransaminasaemia (aspartate aminotransferase 259 UI/mL, alanine aminotransferase 139 UI/mL); and mild lymphocytopenia (1060/mm³). On day 6 post admission, he had a positive result on SARS-CoV-2 RNA RT-PCR (viral load: 4,976,000 copies/mL, 313 copies/100,000 copies RNase P), and was transferred to the Infectious Diseases Unit. Two days later, he underwent chest computed tomography scan which revealed a pattern compatible with viral pneumonia (ground-glass opacities and crazy-paving). To exclude other concomitant causes, he started a diagnostic workup including blood PCR for viral and fungal infections, and several blood cultures. All the microbiological enquiries tested negative. The patient remained febrile, with blood tests showing persistently elevated CRP (up to 7.69 mg/dL) and ferritin (above 1000 µg/L) levels. On day 30 post admission, the patient was administered his replacement therapy with IVIG 30 g, and the following day he retested positive on SARS-CoV-2 RNA RT-PCR using sputum (viral load: 7904 copies/mL, 205 copies/100,000 RNase P) and nasopharyngeal swab (viral load: 1080 copies/mL). On day 31 post admission, he started a 10-day course of remdesivir (200 mg loading dose followed by 100 mg every 24 h). He defervesced after the first dose of remdesivir, and blood tests on the fourth day of remdesivir showed CRP (3.25 mg/dL) and ferritin (527 µg/L) reduced by half and lymphocytic count back to the normal range (1930/mm³). On day 38 post admission (day 8 of antiviral therapy), after giving informed consent, he was administered 1200 mg of casirivimab (REGN10933) and 1200 mg of imdevimab (REGN10987) for compassionate use (Ethical Committee Approval 0003273-U, 29/01/2021) with no side effects. On day 42 post admission, he had a negative result on SARS-CoV-2 RNA RT-PCR using nasopharyngeal swab (quantitative assay showed no detectable viral load), and he was discharged in good clinical condition. Blood tests showed CRP in the normal range (0.80 mg/dL). At follow-up evaluation, 16 days after hospital discharge, the patient tested negative on SARS-CoV-2 RNA RT-PCR using sputum. He remained afebrile and asymptomatic. CRP (0.43 mg/dL), IL-6 (10.3 ng/L) and ferritin (98 µg/L) levels were further reduced.

Discussion

Microbiologic and clinical responses of immunodeficient patients infected with SARS-CoV-2 to remdesivir and other treatments have received little research attention, especially patients with rare primary immunodeficiencies. Regarding patients with XLA, some case reports have described treatment with convalescent plasma, alone or in combination with remdesivir and interleukin inhibitors (Hovey et al., 2020; Jin et al., 2020; Milošević et al., 2020; Mira et al., 2020; Soresina et al., 2020; Iaboni et al., 2021). Intriguingly, some patients with XLA were able to recover from COVID-19 without the need for intensive care or oxygen ventilation, despite the lack of specific antibodies. Currently available data show that SARS-CoV-2 infection may be controlled by a combination of CD4+ and CD8+ T cells without neutralizing antibodies. Nevertheless, a coordinated, early response by all three above-mentioned elements of adaptive immunity is likely to be most successful at controlling infection and limiting the severity of COVID-19. Of note, a recent publication has highlighted how cellular immunity is stable whereas humoral responses wane early during convalescence (Bonifacius et al., 2021). To date, there is conflicting evidence on the efficacy of passive antibody administration in COVID-19, either through transfusion of convalescent plasma or by administration of monoclonal antibodies (mAbs). In a randomized trial of 334 adult patients with severe SARS-CoV-2 pneumo-

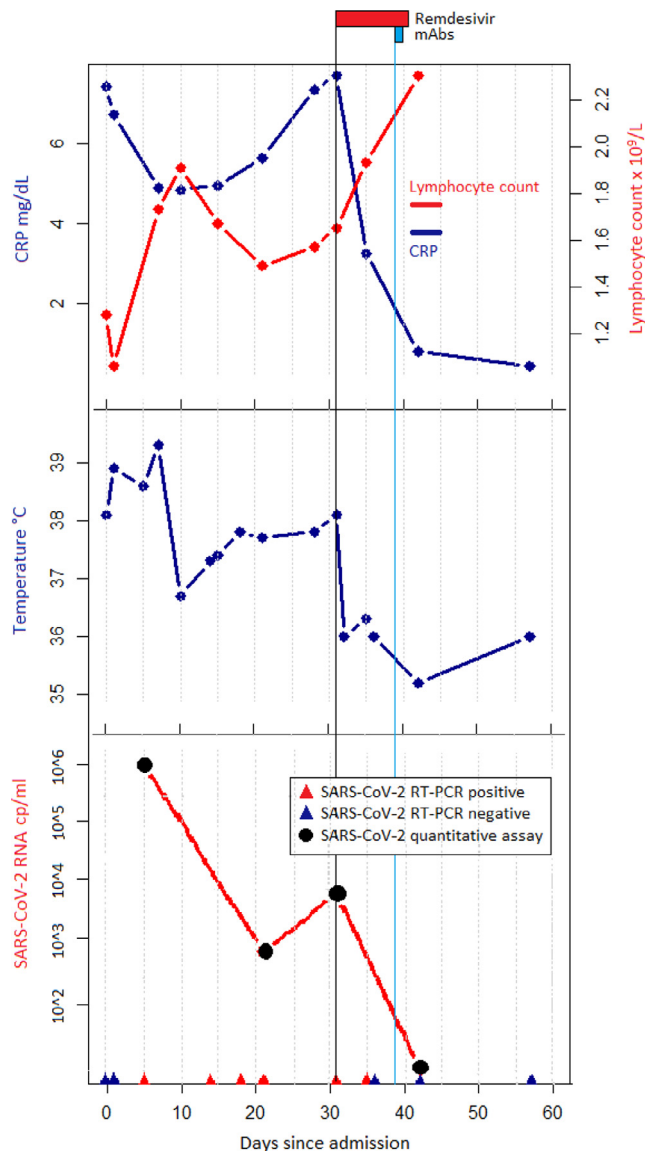


Figure 1. Clinical and virological assessment of the response to remdesivir and monoclonal antibodies. C-reactive protein (CRP), total lymphocyte count, temperature and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) viral load from patient samples, plotted by days since admission, aligned with clinical interventions. Qualitative testing with SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) is marked with red (positive) and blue (negative) triangles.

nia, Simonovich et al. (2021) compared convalescent plasma with placebo, and found no difference in clinical outcome or mortality between the two groups. Use of a combination cocktail of neutralizing mAbs against the spike protein is currently being evaluated in a double-blind, phase 1–3 trial involving 275 non-hospitalized patients with COVID-19 (Weinreich et al., 2021). Interim analysis has shown a reduction in viral load, with a greater effect in patients whose immune response had not yet been initiated (serum antibody-negative) or who had a high viral load at baseline.

There are still no data on the administration of mAbs in patients with humoral immunodeficiency.

This case report presented a case of COVID-19 relapse in a patient with a compromised immune system and recent hospitalization, who benefited from antiviral therapy, achieving clinical recovery and viral clearance. Given the humoral immunodeficiency and the newly detectable viral load, and following the exclusion of other possible concomitant causes, the authors decided to treat

the patient for COVID-19 recurrence, with two aims. First, the viral load was decreased, with administration of a longer course of antiviral therapy; this had been reported to be effective for viral clearance in a patient with XLA (Buckland et al., 2020) and in severely immunocompromised patients (Camprubi-Ferrer et al., 2020; Helleberg et al., 2020). Secondly, a combination cocktail of mAbs was administered once the viral load had been reduced in order to achieve further passive immunization in a patient with an impaired immune response, and reduce the risk of re-infection. The clinical and virological outcomes were achieved, with stable apyrexia and viral clearance. It is acknowledged that the patient received other therapies during his hospitalization, including IVIG. Nonetheless, clinical and laboratory findings, such as resolution of fever and hyperinflammation reduction, along with viral clearance on molecular tests, were linked in a timely manner to remdesivir and mAbs administration, suggesting that the therapeutic choices shaped the favourable outcome in this patient. More importantly, no side effects were reported. The clinical and virological results were sustained; 19 days after mAbs administration and 17 days after the last dose of remdesivir, the patient remained asymptomatic and tested negative on SARS-CoV-2 RNA RT-PCR using sputum. Of note, the follow-up period was within the estimated half-life of mAbs (24 days for 1200 mg REGN10933 and 21 days for 1200 mg REGN10987). The use of passive immunization for the treatment of COVID-19 remains experimental and, as such, it should be monitored carefully. As reported by Kemp et al. (2021), prolonged therapy with convalescent plasma can trigger an evolutionary response by SARS-CoV-2, resulting in the selection of viral variants with reduced sensitivity to neutralizing antibodies. Persistence and accelerated viral evolution have also been described in an immunocompromised patient treated with repeated courses of remdesivir followed by an antibody cocktail against the SARS-CoV-2 spike protein (Choi et al., 2020).

The authors believe that this case shows the potential usefulness of combined therapy with antiviral drugs and mAbs in managing persistent SARS-CoV-2 infection in patients with severe humoral immunodeficiency. Further studies are needed to confirm efficacy and monitor long-term effects on viral variants.

Fig. 1.

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Conflict of interest statement

None declared.

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Ethical approval

Written informed consent was obtained from the patient.

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