

Persistent COVID-19 in an Immunocompromised Patient Temporarily Responsive to Two Courses of Remdesivir Therapy

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The antiviral drug remdesivir has been shown clinically effective for treatment of COVID-19. We here demonstrate suppressive but not curative effect of remdesivir in an immunocompromised patient. A man in his fifties treated with chemoimmunotherapy for chronic lymphocytic leukemia experienced a 9-week course of COVID-19 with high fever and severe viral pneumonia. During two 10-day courses of remdesivir starting 24 and 45 days after fever onset, pneumonia and spiking fevers remitted, but relapsed after discontinuation. Kinetics of temperature, C-reactive protein, and lymphocyte counts mirrored the remitting/relapsing SARS-CoV-2 infection. Combination therapy or longer treatment duration may be needed in immunocompromised patients.

Keywords. COVID-19; SARS-CoV-2; remdesivir; immunocompromised; case report.

The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a huge burden of morbidity and mortality worldwide. Recently, preliminary results of the Adaptive COVID-19 Treatment Trial (ACTT), a multicenter randomized controlled trial of remdesivir versus placebo for treatment of coronavirus disease 2019 (COVID-19) in hospitalized patients, demonstrated that remdesivir reduced time to recovery, in particular for those not yet having experienced respiratory failure with need for assisted ventilation [1]. Despite clinical benefit, there was still a substantial mortality rate, especially among patients with underlying risk factors.

We here report the clinical course and findings in an immunocompromised patient with remission of COVID-19 during

treatment with remdesivir but relapse soon after discontinuation. This pattern was repeated during and after a second course of remdesivir treatment.

METHODS

Data were obtained from electronic health records. The diagnosis of COVID-19 was confirmed by polymerase chain reaction (PCR) of throat swabs using the SARS-CoV-2 assay from Roche and the Cobas 6800/8800 system, apart from the first test where an in-house assay was used. Plasma samples were analyzed using chemiluminescent immunoassays-based kits for SARS-CoV-2 IgM/IgG and chemiluminescence analyzer iFlash from YHLO. The patient gave informed consent.

RESULTS

A Caucasian man in his fifties, diagnosed with chronic lymphocytic leukemia (CLL) 2 years prior and treated with 6 cycles of fludarabine, cyclophosphamide, and rituximab ending 3 months prior, presented with spiking fevers, muscle pain, and loss of taste and smell. PCR for SARS-CoV-2 on a throat swab was positive (cycle threshold value 13).

The CLL disease was in complete remission according to the International Workshop on Chronic Lymphocytic Leukemia 2018 criteria, with a remaining low lymphocyte count of $0.8 \times 10^9/L$. He had no other comorbidities, a normal body mass index of 25, and he did not smoke or drink alcohol in excess. Until he presented with the acute infection, he had been in good general condition and worked full time.

COVID-19 was diagnosed the day he started having fevers. At the time of diagnosis, he had no respiratory distress and self-isolated at home. In the following description, days are counted from the onset of fever. The clinical course and key findings are summarized in [Figure 1](#).

On day 14 he was admitted to hospital with a 1-week history of dry cough and a 4-day history of continuous spiking fevers and dyspnea. PCR for SARS-CoV-2 on a throat swap remained positive (quantitation not available). Vital signs and laboratory test results are summarized in [Table 1](#). A chest X-ray showed bilateral interstitial infiltrates. He was treated empirically with piperacillin/tazobactam. During the following days his condition worsened. He needed supplemental oxygen, increasing to 8 L/minute, and blood tests showed severe lymphopenia and elevated biomarkers of inflammation. On day 22 a PCR for SARS-CoV-2 on a throat swap was still positive and a chest X-ray showed progression of the interstitial infiltrates and new consolidating infiltrates. On day 24 he was enrolled in the ACTT trial and was randomized to treatment with placebo or remdesivir for 10 days. After completion of the trial, unblinding

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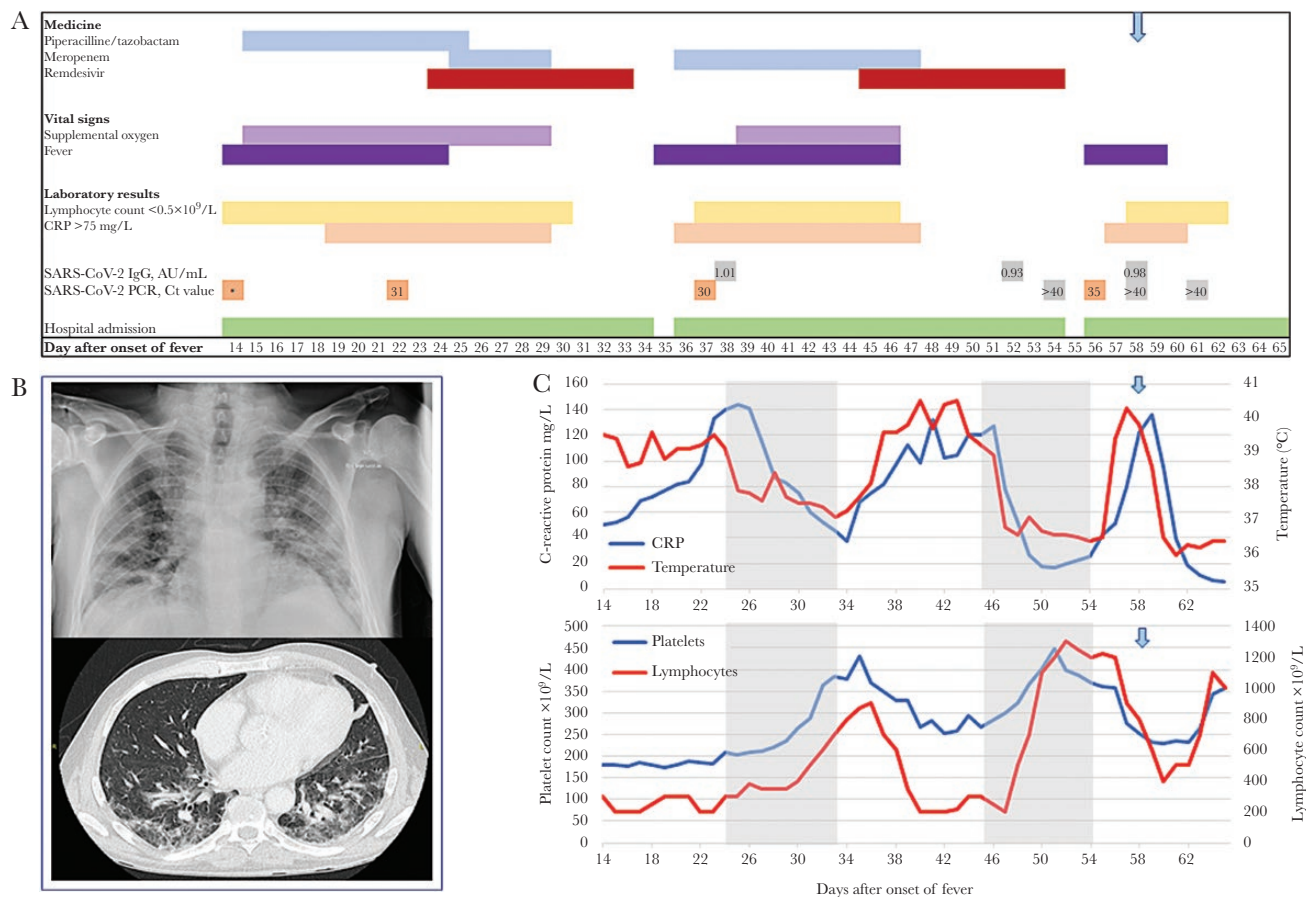


Figure 1. Timeline of hospital admissions, treatments, and tests for SARS-CoV-2 (A); radiology (B); and kinetics of temperature, C-reactive protein, platelet, and lymphocyte counts (C) before, during, and after treatment with remdesivir. A and B, Blue arrows indicate the day of infusion of convalescent plasma. A, Orange boxes for SARS-CoV-2 PCR represent positive tests; grey boxes for SARS-CoV-2 antibody and PCR represent negative tests. *Ct value not available for this test. C, Grey shade indicates the time period of remdesivir treatment. Abbreviations: CRP, C-reactive protein; Ct, cycle threshold; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

showed that he was in the remdesivir arm and had been treated with remdesivir 200 mg intravenous (IV) loading dose followed by 100 mg IV every day. Two days after the initiation of remdesivir, the fever abated and his general condition improved. He continued to improve and was discharged on day 35 after finishing the 10-day course of remdesivir. Three days after the last dose (day 36), high fevers and dyspnea recurred, and he was readmitted to hospital. SARS-CoV-2 PCR on a throat swab was positive. Cultures of blood, airway secretions, and urine showed no growth and he did not improve on empiric treatment with meropenem. Another course of remdesivir was initiated on day 45 (after completion of the trial). The next day he was afebrile and the following day his general condition improved. Markers of inflammation that had increased after discontinuation of remdesivir decreased again. He received 10 days of treatment with remdesivir. SARS-CoV-2 PCR on a throat swab at the end of treatment (day 54) was negative and he was discharged. The day after discontinuation of remdesivir, the fever recurred once again, and he was readmitted (day 55). SARS-CoV-2 PCR on a

throat swab was again positive. This time he was not in respiratory distress and did not need supplemental oxygen. However, he had fever with temperatures $> 40^\circ\text{C}$ and complaint of general malaise and on day 58 he received an infusion of 2×270 mL convalescent plasma IV. From day 60 he was afebrile and biomarkers of inflammation were improving. On day 65 he was in good general condition and discharged from hospital. The patient did not receive corticosteroids during the course of the disease.

Tests for SARS-CoV-2 antibodies on days 38, 52, and 58 were negative. He had received a 7-valent conjugate pneumococcal vaccine followed by a 23-valent polysaccharide vaccine in 2018, but a test for pneumococcal antibodies during the second admission showed that he had no antibodies and thus no vaccine response.

DISCUSSION

SARS-CoV-2 can cause a range of disease manifestations, from asymptomatic infection through mild to severe disease,

Table 1. Vital Signs and Results of Blood Tests, Microbiological and Radiological Examinations at Time of Hospital Admissions, and Time of Initiation of Remdesivir

| Test | 1st Hospital Admission | Start of 1st Course of Remdesivir | 2nd Hospital Admission | Start of 2nd Course of Remdesivir | 3rd Hospital Admission |
|---|-------------------------------------|--|---|--|---------------------------------|
| Vital signs | | | | | |
| Temperature, °C | 39.3 | 38.4 | 38.1 | 39.4 | 39.3 |
| Respiratory rate/min | 26 | 24 | 24 | 22 | 12 |
| Oxygen saturation, % | 96 | 93 | 91 | 92 | 97 |
| Supplemental oxygen, L/min | 0 | 8 | 0 | 2 | 0 |
| Pulse, rate/min | 94 | 72 | 103 | 92 | 95 |
| Blood pressure, mmHg | 125/85 | 120/60 | 120/85 | 110/70 | 125/85 |
| Weight, kg | 84.9 | 84.6 | 81.5 | 78.5 | 82.7 |
| Laboratory tests | | | | | |
| Hemoglobin, mmol/L (ref 8.3–10.5) | 8.8 | 7.8 | 7.2 | 6.4 | 6.2 |
| Leucocyte count $\times 10^9/L$ (ref 3.5–8.8) | 0.8 | 2.5 | 7.0 | 2.5 | 6.2 |
| Neutrophil count $\times 10^9/L$ (ref 1.6–5.9) | 0.3 | 1.3 | 4.9 | 1.5 | 3.6 |
| Lymphocyte count $\times 10^9/L$ (ref 1.0–3.5) | 0.3 | 0.3 | 0.7 | 0.3 | 1.2 |
| Platelet count $\times 10^9/L$ (ref 145–390) | 181 | 209 | 368 | 267 | 341 |
| Creatinine, $\mu\text{mol/L}$ (ref 60–105) | 80 | 70 | 78 | 55 | 59 |
| ALT, U/L (ref 10–70) | 56 | 66 | 26 | 65 | 36 |
| Lactate dehydrogenase, U/L (ref 105–205) | 252 | 299 | 191 | 266 | 220 |
| C-reactive protein, mg/L (ref <10) | 50 | 140 | 75 | 120 | 26 |
| Ferritin, $\mu\text{g/L}$ (ref 12–300) | 1030 | 1780 | 1060 | 2530 | 990 |
| D-dimer, FEU/L (ref <0.6) | <0.3 | <0.3 | 0.3 | 0.4 | <0.3 |
| Fibrinogen, $\mu\text{mol/L}$ (ref 5.3–10.3) | ND | >22 | ND | >22 | >22 |
| Troponin T, ng/L (ref <14) | <13 | ND | ND | ND | <13 |
| Microbiology | | | | | |
| Blood culture | Negative | | Negative | | Negative |
| Sputum culture | Negative | | Negative | | |
| Urine culture | Negative | | Negative | | Negative |
| Blood PCR for HSV, VZV, CMV, EBV | Negative | | | Negative | Negative |
| Radiology | | | | | |
| Chest X-ray | Bilateral, interstitial infiltrates | Progression of interstitial infiltrates New consolidating infiltrates | Unchanged interstitial infiltrates, slight improvement of consolidating infiltrates | | Unchanged bilateral infiltrates |
| Chest CT-scan | | | | Widespread, bilateral ground-glass changes, interstitial infiltrates and consolidating infiltrates No pulmonary embolism | |

Abbreviations: ALT, alanine aminotransferase; CMV, cytomegalovirus; CT, computed tomography; EBV, Epstein Barr virus; FEU, fibrinogen equivalent unit; HSV, herpes simplex virus; ND, not determined; ref, reference; VZV, varicella zoster virus.

but there is typically resolution of the infection within 1–3 weeks after the onset of symptoms in the immunocompetent host [2]. The pathogenesis of severe disease is not well elucidated. Critical illness in COVID-19 is characterized by high

fever and significantly elevated biomarkers of inflammation and is thought to be caused by an aberrant hyperactivated immune response and cytokine storm [3], but there is also emerging evidence that preexisting immunocompromise is

associated with a significantly increased risk of severe disease [4, 5]. The role of ongoing viral infection versus a secondary hyperreactive immune response in the aftermath of viral replication for the development of severe COVID-19 is not completely understood [6].

We present a case of severe COVID-19 in a patient with B- and T-lymphocyte impairment secondary to CLL treated with chemoimmunotherapy 3 months prior to the SARS-CoV-2 infection. Biomarkers and repeated positive PCR tests for SARS-CoV-2 indicated continuous viral replication for up to 9 weeks. Both the spiking fever, dyspnea, and abnormalities in biomarkers of inflammation resolved during treatment with the antiviral drug, remdesivir, but there was relapse soon after discontinuation of treatment. When treatment was resumed, the symptoms and signs of inflammation abated once again (Supplementary Figure 1). Only a day after the second course of remdesivir had finished, the fever recurred, and abnormalities of blood tests worsened but this time the disease was milder. These observations indicate that remdesivir suppressed viral replication but was unable to eradicate the infection. The convincing effect of remdesivir also argues for ongoing viral replication being an important driver of disease manifestations in this immunocompromised patient. However, due to the lack of quantitative viral load measurements, analyses of viral outgrowth, and sampling from the lower respiratory tract we cannot draw any firm conclusions.

A large multicenter randomized controlled trial of remdesivir versus placebo for COVID-19 in hospitalized patients showed that remdesivir reduces time to recovery significantly, with the largest effect size among patients requiring supplemental oxygen but not invasive or noninvasive mechanical ventilation [1]. In this subgroup, there was also a significant reduction in mortality. The patient we here describe belonged to this subgroup at the time of randomization. The optimal duration of treatment with remdesivir in immunocompetent as well as immunocompromised patients remains to be defined. Of note in the ACTT study, a suggestion of a survival benefit for patients with advanced disease dissipated in the days following completion of an initial 10-day treatment course [1].

Therapies combining remdesivir with another antiviral drug or an immune modulator may reduce risk of treatment failure and improve treatment outcomes. Randomized controlled trials employing this treatment strategy are underway. Our patient was treated with convalescent plasma when he experienced the second relapse after treatment discontinuation, because remdesivir was not available at that time. He recovered in the following days. Whether he recovered spontaneously or due to treatment with convalescent plasma is unknown.

The immunological mechanisms for control of SARS-CoV-2 infection in humans have not yet been clearly elucidated. Both cytotoxic T cells and antibody-mediated immune responses may be important for clearance of the viral infection [7].

Convalescent or hyperimmune immunoglobulins for treatment of COVID-19 are currently being tested in clinical trials, although the clinical beneficial effects hereof remain uncertain [8]. The patient described in this report had not developed SARS-CoV-2 antibodies 8 weeks after the infection was diagnosed by PCR. CLL is associated with B-lymphocyte impairment as well as a general immune dysfunction, leading to increased risk and severity of infections [9]. Solid organ transplant recipients, who primarily have compromised T-lymphocyte function, are also at significantly increased risk of severe COVID-19 [10]. But in general, comprehensive data on the outcome of COVID-19 in patients with various types of immune deficiencies are still scarce.

It is difficult to determine the duration of ongoing viral infection using routine clinical laboratory methods. Viral RNA can be detected in biological samples by PCR for several weeks after resolution of symptoms when replication-competent virus can no longer be detected by viral cell cultures [11, 12]. There is correlation between the viral load as determined by quantitative PCR and results of viral cell cultures [11, 12]. However, viral culture assays may have suboptimal sensitivity and a negative culture does not necessarily rule out that replication-competent virus is present [13].

We did not have access to a validated quantitative PCR for SARS-CoV-2 and therefore only qualitative PCR was performed. Viral cultures were not available. Also, in patients with COVID-19 pneumonia, the virus may only be detected in the lower respiratory tract [14], suggesting that the sampling we did from the pharynx may not have focused on the location of viral replication (ie, the lungs).

There was close correlation between subjective symptoms, kinetics of body temperature, levels of C-reactive protein, and the lymphocyte and platelet counts in relation to treatment with remdesivir. These dynamic changes were most likely causally related to the provision of the antiviral medication. The patient was unresponsive to empiric antibacterial therapy and extensive and repeated microbiological examinations failed to identify other pathogens.

Decreased lymphocyte counts have consistently been reported in SARS-CoV-2 and other viral infections [15]. The rapid recovery of lymphocyte counts during and immediately after antiviral therapy seen in this case suggests that the lymphopenia is caused by redistribution of lymphocytes from the peripheral blood to inflamed tissues and not by lymphocytes being killed as a result of the infection.

CONCLUSION

The course and findings in this clinical case suggest that remdesivir has a rapid onset of action and can suppress, but may not eradicate, SARS-CoV-2 in immunocompromised patients. There is a need for development of additional treatments to improve outcomes as well as consideration for longer

treatment courses with remdesivir in certain subgroups of patients.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Author contributions. All authors collected data and participated in data interpretation. M. H. wrote the first draft of the paper and all authors participated in writing subsequent drafts. M. H. and K. S. M. produced the figures. All authors approved the final version of the manuscript. J. L. and C. L. designed and had oversight of the parent study.

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