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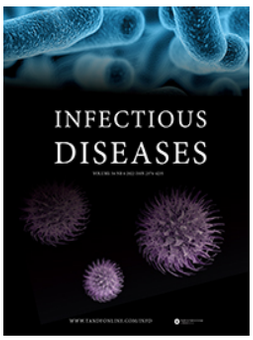
2022-06-03

Kajova , M , Kekäläinen , E , Anttila , V-J & Paajanen , J 2022 , ' Successful treatment with a short course of remdesivir in a case of prolonged COVID-19 in a lymphoma patient ' , Infectious Diseases , vol. 54 , no. 6 , pp. 455-459 . https://doi.org/10.1080/23744235.2022.2028896

http://hdl.handle.net/10138/343288
https://doi.org/10.1080/23744235.2022.2028896



Infectious Diseases

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/infd20

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**To cite this article:** Mikael Kajova, Eliisa Kekäläinen, Veli-Jukka Anttila & Juuso Paajanen (2022) Successful treatment with a short course of remdesivir in a case of prolonged COVID-19 in a lymphoma patient, Infectious Diseases, 54:6, 455-459, DOI: 10.1080/23744235.2022.2028896

**To link to this article:** https://doi.org/10.1080/23744235.2022.2028896

Taylor & Francis
Taylor & Francis Group

INFECTIOUS DISEASES,
2022; VOL. 54,
NO. 6, 455–459

https://doi.org/10.1080/23744235.2022.2028896

CASE REPORT

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# Successful treatment with a short course of remdesivir in a case of prolonged COVID-19 in a lymphoma patient

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## ABSTRACT

**Background:** Patients with haematological malignancies have an increased susceptibility for COVID-19 and higher mortality. They may also have prolonged symptoms and viral shedding. Clinical trials have not specifically addressed the management of this patient group. We present a lymphoma patient with COVID-19 who was treated with remdesivir, and a literature review of similar cases.

**Methods:** SARS-CoV-2 RT-PCR, virus culture and whole-genome sequencing were performed from nasopharyngeal swabs and antibody testing from serum. In addition, SARS-CoV-2 nucleocapsid antigen was tested from serum. Medline was searched for reported cases of lymphoma and COVID-19 treated with remdesivir.

**Results:** The patient was undergoing lymphoma treatment including chemotherapy, rituximab and prednisolone. After diagnosis of COVID-19, broad-spectrum antibiotics were administered due to neutropenia and fever. After 20 d of fever with no signs of co-infection, remdesivir was initiated with rapid response. The treatment was continued for 4 d. Serum SARS-CoV-2 antibody tests were negative 20, 30 and 66 d from symptom onset. Before starting remdesivir, the SARS-CoV-2 PCR and virus culture from the nasopharynx and serum antigen test were positive. From earlier reports, we identified a total of eleven cases of lymphoma and COVID-19 treated with remdesivir accompanied by other antivirals and anti-inflammatory agents.

**Conclusions:** As shown in this and earlier reports on lymphoma patients, the clinical course of COVID-19 may be protracted and a humoral immune response may remain absent. In addition, optimal management remains undecided. The presented patient responded well to a short course of remdesivir.

**KEYWORDS**
COVID-19
lymphoma
remdesivir

**ARTICLE HISTORY**
Received 3 November 2021
Revised 29 December 2021
Accepted 7 January 2022

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Supplemental data for this article can be accessed here.

## Introduction

There is considerable variation in the risk that SARS-CoV-2 poses on different groups of people; those with haematological malignancies are more susceptible to infection and have higher mortality compared to the general population [1,2]. Immunocompromised patients may shed the virus for long periods of time [3]. We present a lymphoma patient with COVID-19 who received remdesivir treatment, accompanied by a literature review of similar cases.

## Materials and methods

All tests were performed in an accredited laboratory (HUS Diagnostic Centre, HUSLAB Clinical Microbiology, Helsinki, Finland). The SARS-CoV-2 RT-PCR test from respiratory samples and serological testing are in routine clinical use at our hospital, and have been described earlier [4,5]. To ensure higher specificity, a combination of two tests was used to detect antibodies targeted against both spike (SARS-CoV-2 IgG ELISA, Euroimmun, Germany) and nucleocapsid (Abbott SARS-CoV-2 IgG CLIA assay, Abbott, IL) proteins [5].

A commercially available test, Salocor SARS-CoV-2 Antigen Quantitative Assay Kit© 23 (Salofa Ltd, 24 Salo, Finland), was used for nucleocapsid antigen testing from serum; a report on test performance is currently available in preprint [6]. The virus was cultured in Vero E6 cells and whole-genome sequencing was performed, as described earlier [4].

A systematic literature review was performed to identify reported outcomes of lymphoma patients treated with remdesivir for COVID-19. The search was conducted in Medline on 19 May 2021. Two authors (M.K and J.P) carried out the initial search using the search terms 'covid' and 'lymphoma'. The exclusion criteria were (1) English translation not available; (2) insufficient information on outcomes; (3) not related to active COVID-19 or lymphoma; (4) remdesivir not used.

## Results (case presentation)

A 46-year-old woman presented to hospital on the day of onset of fever. Her nasopharyngeal swab sample tested positive for SARS-CoV-2 and sequencing revealed the B.1.1.7 variant. During the preceding 4 d, she had experienced mild symptoms including sore throat, runny nose and cough. Seven weeks earlier she had been diagnosed with stage IVA CD5-negative small-cell lymphoma with suspected transformation based on extensive radiologic findings. The lymphoma had been treated with two cycles of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP), a third cycle including etoposide (R-CHOEP) and high-dose methotrexate twice. She had ongoing trimethoprim-sulfamethoxazole prophylaxis against *Pneumocystis jirovecii* and subcutaneous dalteparin treatment for deep vein thrombosis. She had not received a COVID-19 vaccine.

The clinical course of our patient is presented in Figure 1. The COVID-19 symptoms began one day after R-CHOEP during prednisolone treatment. Upon hospital admission, she had fever and tachycardia, but was normotensive and did not develop organ dysfunction. The laboratory work-up showed severe neutropaenia, for which granulocyte colony stimulating factor treatment was administered, as well as lymphocytopaenia and thrombocytopaenia. A chest X-ray showed minor bilateral infiltrates in lower lung fields consistent with viral pneumonitis.

Empirical antimicrobial therapy with cefepime was initiated due to fever and neutropaenia, followed by vancomycin and ciprofloxacin after anaphylaxis, these were later changed to levofloxacin. Physical examinations showed no signs of bacterial foci, and cultures of blood and urine were negative. A computed tomography scan of the chest, abdomen and pelvis showed residual lymphoma findings and bilateral, peripheral, ground-glass opacities consistent with COVID-19 pneumonia, without suspicion of bacterial superinfection. Levofloxacin was discontinued.

The patient had persistent fever for over 2 weeks, accompanied by fatigue, dyspnoea on exertion and diarrhoea. She had mild hypoxaemia with intermittent need for supplemental oxygen. A SARS-CoV-2 PCR test from a nasopharyngeal swab sample 19 d after the onset of symptoms was positive, but based on cycle threshold values and virus culture, the viral load was decreasing (Supplementary material). A serum antigen test for SARS-CoV-2 was positive before remdesivir treatment 20 d from the onset of symptoms. SARS-CoV-2 antibodies were negative after 20, 30 and 66 d of symptoms.

Intravenous remdesivir was commenced after 20 d of symptoms with a 200 mg loading dose and the patient soon became afebrile. The treatment was continued 100 mg daily for three more days, after which she was discharged in good overall condition. Although 5 d treatment duration was generally recommended, in this case 4 d was considered adequate due to rapid recovery.

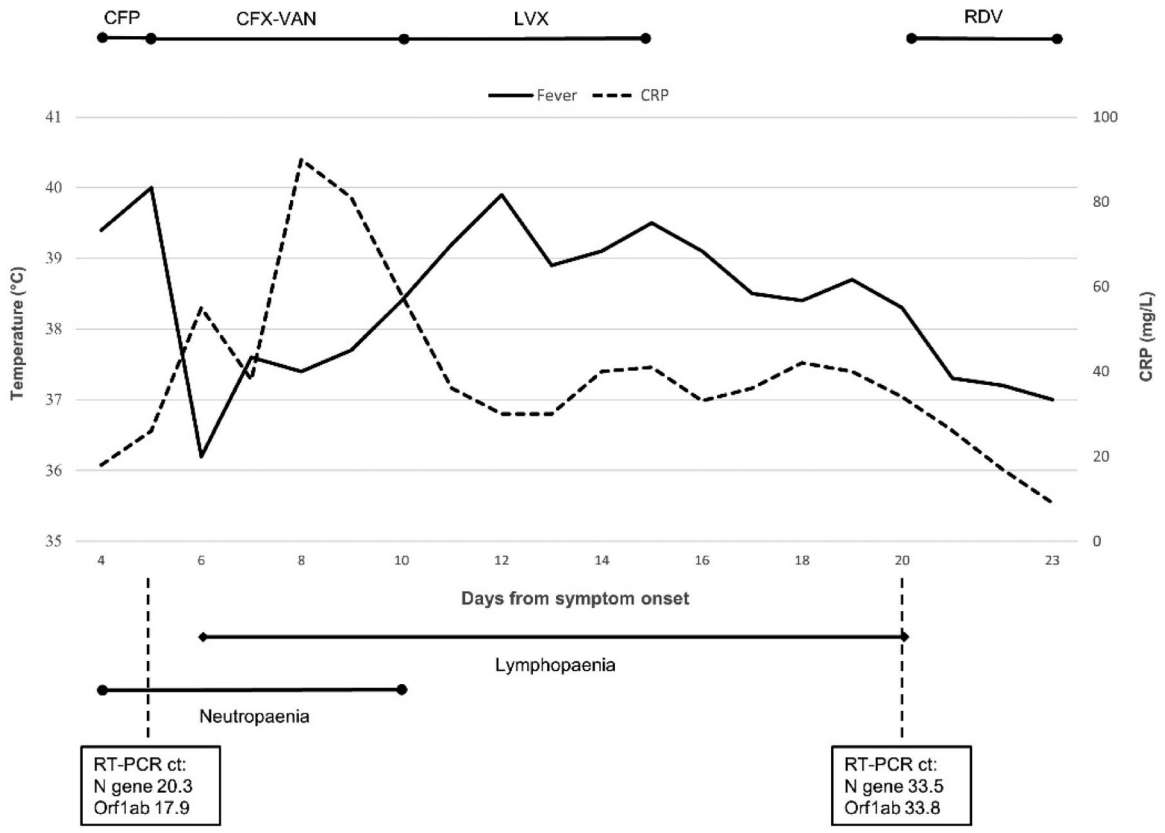


**Figure 1.** Clinical course of the SARS-CoV-2 infection following chemotherapy and rituximab treatment for lymphoma. CFP, cefepim; CFX, ciprofloxacin; VAN, vancomycin; LVX, levofloxacin; RDV, remdesivir. Neutropaenia: neutrophils $<1.0 \times 10^9$/l; Lymphopaenia: lymphocytes $<1.0 \times 10^9$/l. RT-PCR cycle threshold (ct) values representing an inverse of viral load given for nasopharyngeal swab samples taken on days 5 and 20.

In the literature review, a total of 227 articles were found and eleven cases were included (Table 1) [7–16].

## Discussion

There is a wide range of clinical manifestations of COVID-19, and the risk of mortality depends on age, sex, comorbidities and individual immune responses [2,17,18]. In comparison to immunocompetent patients, those with haematological malignancies can have more protracted symptoms, including delayed respiratory failure or relapse even months later [7,16,18–20]. In a recent study, anti-CD20 therapy such as rituximab was associated with a longer hospital stay and increased mortality [21].

Our patient had a positive serum SARS-CoV-2 antigen test consistent with viraemia 20 d after the onset of symptoms, although we were not able to test for live virus in the blood. However, virus culture from a nasopharynx swab was positive. In earlier reports, immunocompromised patients have shed live virus for months [3,7]. Therefore, COVID-19 in severely immunocompromised hosts may present both with persistent viral replication and an atypical clinical course.

A functioning adaptive immune response including humoral and cellular immunity is considered important for efficient clearance of SARS-CoV-2 infection. Circulating antibodies are usually detected within 15 d after infection onset, but our patient failed to develop a humoral response probably due to prior rituximab therapy [17]. However, recovery is achievable without seroconversion and in earlier studies 1–9% of PCR-confirmed cases have remained seronegative, which underlines the role of T cell responses in clearing the virus [17].

Remdesivir has been shown to inhibit the replication of coronaviruses including SARS-CoV-2 *in vitro* [22]. The ACTT-1 trial demonstrated a shorter time to recovery in the remdesivir group compared to placebo among hospitalized COVID-19 patients [23]. Currently there is, however, a lack of evidence from clinical trials for mortality benefit in the treatment of hospitalized patients [22,24]. Timing may be important, as antivirals are expected to be efficacious only in the viral replication phase [22]. Indeed, a recent randomized controlled trial showed remdesivir to be efficacious in preventing hospitalization

**Table 1.** Previously reported lymphoma patients treated with remdesivir for COVID-19.

| References | Age (years) | Sex | Lymphoma subtype | Ongoing lymphoma treatment | Approx. clinical duration of COVID-19 (days) | COVID-19 treatments (initiation day from symptom onset) | SARS-CoV-2 serology (days from symptom onset)[a] | Latest positive RT-PCR or culture (days from symptom onset) | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| [7] | 60 | M | MCL | CYC, DOX, PRD, anti-CD20 and B-cell antibodies | 131 | RDV (30 and 122)<br>CP (31 & 122) | Negative (30, 120,124,127)<br>Positive (66, 88,122) | 119 (culture) | Resolved |
| [8] | 37 | F | FL | ETO, CIS, CYT, MET, RIT | 60 | LOP/RIT, HCQ, AZM, DAR/COB, RDV (28, 55), MET, ANA, IVIG (46, 61), CP (64) | Negative (42, 64) | 60 (PCR) | Resolved |
| [9] | 53 | F | FL | OBI maintenance | 90 | RDV (63, 81), CP (86) | Negative (approx. 90) | 90 (PCR) | Resolved |
| [10] | 60 | M | MCL | RIT maintenance | >100 | HCQ, LOP/RIT, MET, TOC, ANA, RDV, CP (78) | Negative (approx. 100) | Approx. 100 (PCR) | Resolved |
| [11] | 43 | M | MCCHL | BRE, DOX, VIN, DAC | 29 | FAV, CIC, RDV (21) | | 14 (PCR) | Resolved |
| [12] | 53 | M | DLBCL | RIT maintenance | 109 | DXM,CP (48, 105),RDV (55) | Negative (98) | 129 (PCR) | Resolved |
| [13] | 51 | F | NHL | RIT maintenance | 230 | TCZ, HCQ, IVIG, COR, RDV | Negative (NA) | 230 (PCR) | Deceased |
| | 67 | M | NHL | NA | 45 | IVIG, RDV, CP, COR | Negative (NA) | 43 (PCR) | Deceased |
| [14] | 47 | F | BL | RIT | 47 | AZM, RDV, CP (45) | Negative (NA) | 45 (PCR) | Resolved |
| [15] | 58 | F | LBL | None | NA | PRD, RDV | NA | NA | Resolved |
| [16] | 56 | F | FL | RIT, BEN | 160 | RDV, CP, INF | Negative (37)<br>Negative (approx. 140) | Approx. 140 (PCR) | Resolved |

RT-PCR: reverse transcription-polymerase chain reaction; MCL: mantle-cell lymphoma; CYC: cyclophosphamide; DOX: doxorubicin; PRD: prednisone; COR: low-dose corticosteroid; RDV: remdesivir, CP: convalescent plasma; FL: follicular lymphoma, RIT: rituximab; ETO: etoposide; CIS: cisplatin; CYT: cytarabine; MET: methylprednisolone; LOP/RIT: lopinavir/ritonavir; HCQ: hydroxychloroquine; AZM: azithromycin; DAR/COB: darunavir/cobistat; ANA: anakinra; IVIG: intravenous immunoglobulins; OBI: obinutuzumab; TOC: tocilizumab; MCCHL: mixed cellularity classical Hodgkin lymphoma; BRE: brentuximab vedotin; VIN: vinblastine; DAC: dacarbazine; FAV: favipiravir; CIC: ciclesonide; DLBCL: diffuse large B-cell lymphoma; DXM: dexamethasone; NHL: non-Hodgkin lymphoma; NA: not available; BL: Burkitt's lymphoma; LBL: T-lymphoblastic lymphoma; BEN: bendamustine; INF: infliximab.

[a]Positive serology results are not shown if antibodies were detected only after administration of convalescent plasma.

when given to outpatients within 7 d of symptom onset [25]. Remdesivir has been granted a conditional marketing authorization for COVID-19 treatment by the European Medicines Agency, but as of now is not in routine clinical use in Finland.

We are not aware of randomized controlled trials addressing COVID-19 management in patients with haematologic malignancies, and such data may be difficult to obtain. Efficient treatment options would be crucial, especially due to inadequate COVID-19 vaccine responses in this subgroup [26]. In case reports, lymphoma patients have appeared to benefit from treatment with convalescent plasma or antivirals such as remdesivir, some requiring repeated treatment cycles (Table 1) [7–9,20]. Although we cannot rule out spontaneous recovery of our patient in due course, we did observe an excellent response to remdesivir. A shortened duration of infection may also be valuable, especially in patients urgently needing next cycles of lymphoma treatment.

To conclude, a prolonged duration of viral replication among immunocompromised patients is noteworthy from the perspective of infectiousness and may indicate benefit from antiviral therapy at a later stage than for other patients. With respect to COVID-19, patients with haematological malignancies are clearly a vulnerable group requiring special attention.

## Acknowledgements

The authors thank Hanna Jarva for advice and help with the microbiological analyses.

## Disclosure statement

V-J.A. has received lecture fees from Pfizer, MSD, Astellas, Unimed, Roche, Biogen, and participated in studies supported by Pfizer and GSK. E.K. has received lecture and consultation fees from Merck, Janssen-Cilag and AstraZeneca. None of the interests listed above are relevant to the current manuscript. M.K. and J.P. declare no conflict of interest.

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