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CASE REPORT

Remdesivir in Coronavirus Disease 2019 patients treated with anti-CD20 monoclonal antibodies: a case series

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Abstract

Purpose COVID-19 patients on anti-CD20 treatment can suffer a delayed viral clearance and worse clinical outcome. We aim to present our experience with remdesivir treatment in anti-CD20-treated patients with prolonged symptoms, a patient population for which no data from randomized controlled trials are available.

Methods From the beginning of the pandemic until February 2021, we included all consecutive patients from our healthcare network on anti-CD20 treatment with prolonged COVID-19 symptoms, who received remdesivir. Patient informed consent was gathered and patients' charts were reviewed to collect baseline data, COVID-19 history including time of symptom onset, diagnosis, data on treatment and disease course. Patients or their next of kin were contacted in March 2022 to assess long-term outcomes.

Results We included 11 patients, who received remdesivir at a median of 33 days after diagnosis. Eight patients showed clinical improvement along with reductions in viral loads, one patient with relapsing infection recovered after administration of convalescent plasma, and two patients died. No clinical relapses were reported (median follow-up 13 months), while follow-up PCRs were not performed. One patient died of underlying malignancy 8 months after recovery from COVID-19.

Conclusions We observed a benefit of antiviral therapy in a majority of COVID-19 patients on anti-CD20 treatment, without any clinical relapses in the 1-year follow-up. Although these data suggest that remdesivir might be a promising management option in patients with delayed viral clearance, the lack of a control group is an important limitation of the study design.

Trial registration Ethikkommission Ostschweiz, Scheibenackerstrasse 4, CH-9000 St. Gallen approved this case series. Project-ID 2021-00349 EKOS 21/027.

Keywords COVID-19 · SARS-CoV-2 · Anti-CD20 antibodies · Rituximab · Remdesivir

Background

Administration of the monoclonal anti-CD20 antibody rituximab has been associated with delayed viral clearance and worse clinical outcome in patients with COVID-19 [1, 2]. Treatment-associated B cell depletion and impaired antibody production following natural SARS-CoV-2 infection and/or vaccination may be the underlying cause of insufficient viral clearance resulting not only in high rates of severe disease but also in COVID-19 recurrence [3–5]. Treatment options in these vulnerable patients are limited. Although antibody-based therapeutics have been suggested to improve the outcome of immunodeficient patients with COVID-19 [6], emerging viral variants are increasingly resistant to many monoclonal antibody compounds [7]. For remdesivir, evidence is controversial. The World Health Organization

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advised against the use of remdesivir in hospitalized patients with COVID-19, regardless of disease severity, based on results from a systematic review and network meta-analysis [8]. However, data show that there is a trend for greater efficacy during the early disease when there is viral replication [9, 10]. In line with these observations, remdesivir has recently been shown to prevent progression to severe COVID-19 in outpatients with underlying risk factors [11]. At the same time, subgroup analyses of the above mentioned studies focused mostly on disease onset and severity, but not on immunosuppressed patients with viral replication [9–11]. Beneficial effects of remdesivir were described in a few patients treated with rituximab [4], who represent a particularly vulnerable patient population with often ongoing viral replication.

We therefore report our experience with the use of remdesivir in patients who had previously received anti-CD20 antibody and presented with relapsing or non-resolving SARS-CoV-2 infection.

Methods

Study design and patient recruitment

In this case series, we included all adult (i.e., 18 years or older) patients with a diagnosis of COVID-19 who were hospitalized within our healthcare network in Eastern Switzerland until February 2021, and who had been treated with anti-CD20 antibodies and received remdesivir. The database of the infectious diseases consult team was used to identify patients. Ethics approval was obtained (EKOS 21/027) and all patients provided informed consent.

Data collection

Medical charts were reviewed for data on comorbidities, immunosuppression, clinical, laboratory and radiologic presentation and course, diagnosis and treatment of COVID-19 and outcome. Cycle threshold (CT) values from PCR tests were provided by the laboratory. All patients discharged alive were contacted by phone 1 year after initial diagnosis to document their health status including any COVID-19 relapse or reinfection.

Laboratory methods

Respiratory samples (200 µl) were extracted with Molgen PurePrep Extraction Kit on an IDEAL96 extraction robot. Nucleic acid extracts were subjected to RT-PCR targeting sequences of the SARS-CoV-2 E-gene, RdRP gene and of the human RNAse P gene as internal amplification and extraction control based on published protocols by Corman et al. [12] and the Centers of Disease Control [https://www.cdc.gov/coronavirus/2019-ncov/lab/rt-pcr-panel-primer-probes.html]. Alternatively, samples were analyzed with the commercial Alinity m SARS-CoV-2 RT-PCR assay on the fully automated Alinity m platform (Abbott Molecular Inc., Des Plaines, USA).

Serum antibodies were determined by commercially available assays (COVID-19 IgG/IgM Rapid Test, Biomerica Inc., Irvine, USA and anti-SARS-CoV-2-ELISA IgG and IgA, Euroimmun, Lübeck, Germany) according to the recommendations of the manufacturers.

Data analysis

Patient characteristics including comorbidities and COVID-19 presentation are described. A timeline showing COVID-19 diagnosis, initiation of remdesivir treatment and the disease course is graphically presented for every patient. To approximate supplemental oxygen values via different applications such as nasal cannula or face masks, we added 4% per L O_2 to 20% (ambient air).

Results

We identified 11 patients treated with anti-CD20 antibodies who were diagnosed with COVID-19 until February 4th 2021 either by SARS-CoV-2 rapid antigen test or PCR (Table 1). Ten patients were hospitalized due to persisting symptoms, whereas one patient (patient number 2) was diagnosed early due to nosocomial infection. In nine patients COVID-19 IgG/IgM serological testing was performed at a median of 26 (range 5–53) days after diagnosis, of whom only one was positive (IgG).

Remdesivir was started at a median of 33 (range 4–87) days after initial diagnosis (Fig. 1). Treatment duration was 5 days for 8 patients, and 10 days for 2 patients. Patient 11 received remdesivir during 17 days given in 3 courses. Co-medications during remdesivir therapy consisted of antibiotics ($n=1$) or steroids ($n=3$) or both ($n=2$). Patient 5 additionally received a single dose of IVIG 3 days prior to remdesivir. All eight febrile patients defervesced at a median of two (range 1–6) days after starting remdesivir. Prior to remdesivir the median CT value (data available from 10 patients) was 24.6, which increased to a median of 29.7 (data available from seven patients) during or within 5 days after treatment. The CT value increased in all four patients who improved and had a subsequent CT value available (Table 2). Supplementary oxygen was given to nine patients at time of first remdesivir dose and was stopped in eight patients at a median of 6.5 days after starting remdesivir.

Eight patients were discharged to home ($n=5$) or rehabilitation ($n=3$) at a median of 6 and 15 days after starting

Table 1 Baseline characteristics of 11 patients on anti-CD20 monoclonal antibodies with COVID-19 treated with remdesivir

Patient identification	1	2	3	4	5	6	7	8	9	10	11
Age (years)	69	80	54	79	51	55	72	52	88	81	45
Sex (male/female)	m	m	f	f	m	f	f	m	f	f	f
Primary disease for which anti-CD20 antibody was given	Lymphoma	Lymphoma	Multiple sclerosis	Limbic encephalitis	Lymphoma	Lymphoma	Mixed collagen vascular disease	Lymphoma	Chronic lymphatic leukemia	Lymphoma	Optic neuromyelitis
Pneumopathy (others)	05/17 Wedge resection due to carcinoma	01/17 Wedge resection due to carcinoma	n	n	n	n	Interstitial pneumopathy and pulmonary artery hypertension	n	n	n	n
Other comorbidities	Adenocarcinoma of the lung	Diabetes, renal insufficiency, asthma; squamous cell carcinoma of the lung	none	Hypertension, diabetes, coronary heart disease	none	Hypertension	Hypertension, carcinoma of the lung (postmortem diagnosed)	None	Hypertension	Hypertension, adenocarcinoma of the lung	None
Anti-CD20 antibody	Rituximab	Rituximab	Rituximab	Rituximab	Rituximab	Rituximab	Rituximab	Obinutuzumab	Obinutuzumab	Rituximab	Rituximab
First dose of anti-CD20 antibody	06.06.2017	22.02.2016	29.08.2016	27.07.2018	18.12.2019	01.09.2014	24.11.2010	18.01.2018	07.09.2020	22.05.2020	01.12.2008
Last dose of anti-CD20 antibody	19.03.2020	09.12.2020	27.08.2020	15.10.2020	20.10.2020	15.10.2020	16.09.2020	06.11.2019	28.12.2020	24.08.2020	21.10.2020

Table 1 (continued)

Patient identification	1	2	3	4	5	6	7	8	9	10	11
Secondary immunoglobulin deficiency	y	y	n	n	y	n	n	n	n	n	n
Intravenous immunoglobulin (date)	n	Y (11.12.2020–23.12.2020)	n	n	Y (22.01.2021)	n	n	n	n	n	n
Additional immunosuppressive agents (date)	Steroids (01.12.2020—04.12.2020)	Steroids (04.01.2021–06.01.2021); Venetoclax (17.12.2020–26.12.2020), Ibrutinib (10/2020–12/2020)	Steroids (04.12.2020–13.12.2020)	Steroids (14.01.2021–23.01.2021)		Steroids (13.12.2020–21.02.2021)	Steroids (15.02.2021–10.03.2021)	Steroids (18.02.2021–22.02.2021)	Chlorambucil (since 05/2019)	Bendamustin (05/2020–09/2020)	
Body mass index (kg/m2)	23.8	26	21.1	26.6	23.3	26	21.6	24.4	20.8	21.5	29.8
Smoking	Previous	Previous	Never	Never	Never	Never	Never	Never	Never	Previous	Never

f female, *m* male, *y* yes, *n* no

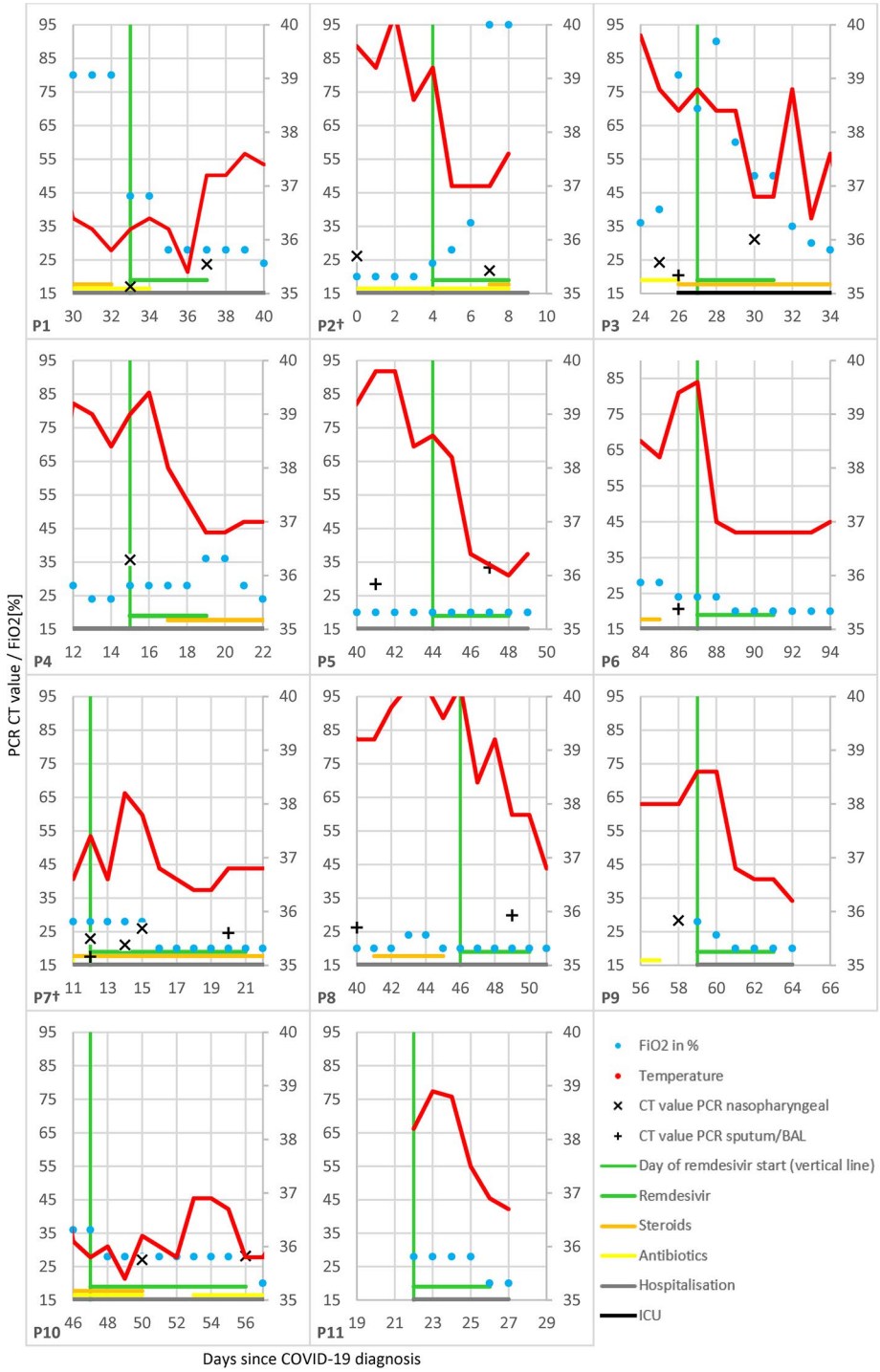

Fig. 1 Clinical course and laboratory findings in eleven COVID-19 patients (P1–P11) treated with anti-CD20 antibodies receiving remdesivir. *x*-axis indicates days since COVID-19 diagnosis. *y*-axis (left) refers to PCR CT values and FiO2 (%); *y*-axis (right) to body temperature in degrees Celsius (FiO2, fraction of inspired oxygen; BAL, bronchoalveolar lavage; ICU, intensive care unit); † death

remdesivir, respectively. Two patients died. Patient 2 died of acute respiratory failure 5 days after starting remdesivir with decreasing CT values (26.2–21.8).

Patient 7 initially improved and was discharged to rehabilitation (CT value increased from 17.6 to 31.4 after 10 days of remdesivir). On day 21, she was readmitted to another hospital due to relapse (CT value 19.2, not shown in Figure) and died 2 days later of respiratory failure. Patient 11 relapsed on day 28 after initial improvement and was retreated with a 10-day course remdesivir, again with good immediate response. However, she suffered from a third relapse on day 52 and received convalescent plasma (CP) yielding stable improvement of symptoms.

At follow-up (median 13 months after initial diagnosis), eight of the remaining nine patients were still alive and no subsequent COVID-19 relapse or reinfection were reported.

Table 2 Cycle threshold (CT) values of SARS-CoV-2 PCR of 11 COVID-19 patients treated with remdesivir

	First initial SARS-CoV-2 test	PCR CT value 1	PCR CT value 2	PCR CT value 3
Patient 1	PCR positive	**17.07**	*23.69*	32.63
Days since start remdesivir	− 33	0	4	14
Specimen	NP	NP	NP	NP
Patient 2	No prior test	**26.17**	*21.81*	
Days since start remdesivir		− 4	3	
Specimen		NP	NP	
Patient 3	Antigen positive	24.26	**20.46**	*31.15*
Days since start remdesivir	− 27	− 2	− 1	3
Specimen		NP	BAL	NP
Patient 4	PCR positive	**35.66**		
Days since start remdesivir	− 15	0		
Specimen	NP	NP		
Patient 5	PCR positive	**28.49**	*33.34*	
Days since start remdesivir	− 44	− 3	3	
Specimen	NP	S	S	
Patient 6	PCR positive	**20.71**		
Days since start remdesivir	− 87	− 1		
Specimen	BAL	BAL		
Patient 7	PCR positive	**17.57**	24.62	*31.43*
Days since start remdesivir	− 12	0	8	13
Specimen	NP	S	S	NP
Patient 8	Antigen positive	**26.21**	*29.91**	
Days since start remdesivir	− 46	− 6	3	
Specimen		BAL	S	
Patient 9	PCR positive	**28.31**		
Days since start remdesivir	− 59	− 1		
Specimen	NP	NP		
Patient 10	PCR positive	**22.96**	27.09	*28.18*
Days since start remdesivir	− 47	− 3	3	9
Specimen	NP	NP	NP	NP
Patient 11	No prior test	25.23*		
Days since start remdesivir		31		
Specimen		BAL		

CT values prior to start or at beginning of remdesivir in bold type (median 24.6). CT values obtained during or within 5 days after treatment marked in italic type (median 29.7). Day of first dose of remdesivir defined as day 0

CT cycle threshold of the E-gene, *NP* nasopharyngeal swab, *BAL* bronchoalveolar lavage, *S* sputum

*N-gene amplification

One patient had died of underlying malignancy 8 months after recovery from COVID-19 (Table 3).

Discussion

This case series describes improvement with remdesivir treatment in 8 of 11 patients with prolonged SARS-CoV-2 replication due to anti-CD20 antibody treatment, even if initiated over a month after initial diagnosis. No clinical relapse was observed within 13 months after initial diagnosis.

We observed a clinical response in most COVID-19 patients with anti-CD20 induced B cell depletion after initiation of remdesivir. These data are in line with several other case reports, showing clinical improvement in response to remdesivir. Remdesivir is an inhibitor of the SARS-CoV-2 RNA polymerase. Therefore, this molecule is expected to only provide clinical benefit in patients with ongoing viral replication. Indeed, it has been shown that COVID-19 patients might particularly benefit from remdesivir if given within 9 days of symptom onset [13]. However, patients treated with anti-CD20 are B cell-depleted and, therefore,

Table 3 Follow up data of survivors

Patient identification	Survival 1 year after discharge	Hospital readmission non-COVID related	SARS-CoV-2 reinfection	Hospital readmission due to COVID relapse/reinfection
1	Yes	No	No	No
3	Yes	Yes	No	No
4	Yes	Yes	No	No
5	Yes	No	No	No
6	Yes	Yes	No	No
8	Yes	No	No	No
9	Yes	No	No	No
10	No (died of underlying malignancy)	Yes	No	No
11	Yes	Yes	No	No

unable to mount a sufficient humoral immune response after SARS-CoV-2 infection or vaccination. Accordingly, SARS-CoV-2 CT values were relatively low in our patients with prolonged symptoms and no SARS-CoV-2-specific antibodies were detected at time of remdesivir initiation in most patients (suggesting ongoing viral replication for much longer than in non-B cell-depleted COVID-19 patients [14]). The increase of CT values along with the rapid clinical improvement subsequent to start of remdesivir suggests a causal relationship in these patients with prolonged symptoms.

Unfortunately, not all patients fared well. One patient died shortly after remdesivir treatment. Retrospectively, treatment was probably initiated too late in this patient. Resistance to remdesivir, as observed by others as cause for remdesivir failure in B cell-depleted patients, was not tested in our patients [15]. Two patients experienced clinical relapses along with drops in CT values. Whereas one of those died, the other one showed good clinical response after administration of CP. However, no further relapses were reported for the remaining patients and all—except for one who died of the underlying malignancy—were still alive after a median of 13 months.

Our observed mortality of 18% is similar (or slightly lower) compared to other reports. In a French cohort of rheumatologic patients, 21% COVID-19 patients under rituximab died compared to 7% in the non-rituximab group [2]. Among 63 patients with non-Hodgkin lymphoma treated with B cell-depleting therapy, 24% died within 30 days compared to 19% among those without such therapy [16]. In a US study including 49 hospitalized and non-hospitalized patients with different underlying comorbidities, 33% died of COVID-19 [17]. These studies did, however, not evaluate the potential beneficial effect of remdesivir.

Besides remdesivir, molnupiravir and nirmatrelvir–ritonavir are novel oral antiviral agents which could potentially be used in this patient population. However, clinical data in patients treated with rituximab are still scarce and both newer antivirals are affected by concerns about mutagenicity or drug interactions, respectively [18]. Favorable patient outcomes have also been described after administration of CP in B cell-depleted COVID-19 patients [19]. Some have suggested to use remdesivir in combination with antibodies, making use of the two distinct mechanisms of action [6]. While monoclonal antibodies have been reported effective in patients with persistent COVID-19 who had received rituximab [20], their effectiveness is increasingly and severely affected by emerging viral variants [7].

We acknowledge that based on our study design causality cannot be inferred between remdesivir use and favorable outcome. Co-administration of other substances, particularly IVIG in one patient, might have biased our results. Furthermore, we cannot exclude the possibility of SARS-CoV-2 reinfection rather than prolonged infection with the same strain. While PCR testing was not performed to confirm viral clearance, the lack of clinical relapse in all surviving patients after a median of 13 months is indicative of effective treatment. Despite these limitations, we think that our experiences are biologically plausible and valuable to physicians caring for COVID-19 patients under rituximab and other anti-CD20 treatments. Duration of therapy might have to be individualized and be guided by clinical and virological response.

Conclusions

We report effective treatment with remdesivir in COVID-19 patients on anti-CD20 treatment with ongoing viral replication. For failing or relapsing patients, antibody-based treatments should be considered as long as the causing viral variant is susceptible. In the absence of randomized controlled trials in this patient population, these data illustrate a promising management option in anti-CD20 treated patients.

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Author contributions SR and PG contributed equally as the first authors, PK and WA contributed equally as the last authors. SR, PG, KB, DF, LK, PK and WA were involved in patient care. SR and PG performed the chart reviews. DG was responsible for viral diagnostics. SR, PK and WA drafted a first version of the manuscript, which was critically appraised by all the authors. SR, PG, PK and WA revised the manuscript.

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Availability of data and materials The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest None of the authors reports any conflict of interest.

Ethics approval Ethikkommission Ostschweiz, Scheibenackerstrasse 4, CH-9000 St. Gallen approved this case series. Project-ID 2021-00349 EKOS 21/027.

Consent for publication Written informed consent to the submission of the case report to the journal was obtained from patients.

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