Multidisciplinary Respiratory Medicine 2022; volume 17:825

pagepress

SHORT REPORT

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SARS-CoV-2 viral load dynamics in immunocompromised critically ill patients on remdesivir treatment

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ABSTRACT

The relationship between SARS-CoV-2 quantitative viral load and risk of disease progression, morbidity such as long-COVID or mortality in immunosuppressed, remains largely undefined in COVID-19 patients. Critically ill immunosuppressed patients potentially benefit from remdesivir treatment because of the prolonged course of their infection. Four critically ill immunocompromised patients and the impact of remdesivir on viral dynamics in lower respiratory samples were studied. Bronchoalveolar lavage (BAL) samples were assessed to measure SARS-CoV-2 quantitative viral load using real-time PCR. Corresponding plasma levels of remdesivir and its metabolite GS-441524 were determined. Mean virus load of 39.74 x 10^7 geq/ml (±33.25 x 10^7 geq/ml) on day 1 dropped significantly ($p<0.008$) to 3.54 x 10^6 geq/ml (±6.93 x 10^6 geq/ml) on day 3 and to 1.4 x 10^5 geq/ml (±2.35 x 10^5 geq/ml) on day 5 of remdesivir treatment. Mean virus load dropped below <1% between day 1 and 5 of remdesivir treatment. Parent prodrug remdesivir and also GS441524 metabolite levels of antiviral activity in our patients were far in excess of EC 50. Our data present that remdesivir treatment potentially reduces the SARS-CoV-2 viral load in immunosuppressed critically ill patients. However, the implication of viral load reduction on morbidity and mortality needs further investigation.

Key words: Remdesivir; COVID-19; immunosuppression; viral load; SARS-CoV-2.

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Contributions: TL, SR, study concept; TL, JE, JRW, SR, contribution to data acquisition; TL, JE, SR, data analysis and interpretation; TL; manuscript drafting; RMS, JS, JRW, CDS, PL, FS, MK, SR, manuscript critical revision for important intellectual content. All authors agree with the article submission. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: T.L. received travel grants and lecture fees from Pfizer and Gilead. Christoph Spinner reports grants, personal fees, and non-financial support from AbbVie; grants, personal fees, and non-financial support from Apeiron; grants, personal fees from B. Braun Melsungen, grants from Cepheid, personal fees from Formycon, grants, personal fees, and non-financial support from Gilead Sciences; grants and personal fees from Eli Lilly; grants, personal fees, and non-financial support from Janssen-Cilag; personal fees from Molecular partners, grants, personal fees, and non-financial support from GSK/ViiV Healthcare; grants, personal fees, and non-financial support from MSD, outside the submitted work. The other authors declare no conflict of interest.

Availability of data and material: All relevant data are made available in the manuscript.

Ethics approval and consent to participate: The Ethics Committee of the Technical University of Munich approved the protocol of this retrospective study and waived the need to obtain consent for the collection, analysis, and publication of the data (approval 807/20S).

Introduction

Immunocompromised critically ill COVID-19 patients are at maximum risk of mortality, due to a dysregulated immune response to the infection and this subgroup of patients has been underrepresented in recent studies. Although the new antiviral drug molnupiravir is promising, treatment of SARS-CoV-2 by an antiviral small molecule is still limited to remdesivir [1]. The relationship between SARS-CoV-2 quantitative viral load and risk of disease progression, morbidity such as long-COVID or mortality in immunosuppressed, remain largely undefined in COVID-19 patients [2,3]. Remdesivir acts as an inhibitor of viral RNA dependent RNA polymerases, originally developed to combat Ebola. In the early phase of the pandemic, remdesivir was authorized for emergency use in patients with severe SARS-CoV-2 infection and received full FDA approval in October 2020.

Although currently not generally recommended for critically ill patients, immunosuppressed potentially benefit from remdesivir treatment because of the prolonged course of their infection.

Patients and methods

Four critically ill, mechanically ventilated, immunocompromised patients and the impact of remdesivir on viral dynamics in lower respiratory samples were studied.

The study was approved by the Institutional Review Board, Klinikum rechts der Isar, Technical University of Munich (Ref. 807/20S). Bronchoalveolar lavage (BAL) samples were assessed on day 1, 3, 5, 10 and 14 of the remdesivir treatment regimen (200 mg on day 1, followed by 100 mg for day2-5; all patients received 6mg dexamethasone for 10 days) to measure SARS-CoV-2 quantitative viral load using real time PCR (RT-PCR).

Anti-SARS-CoV-2-IgG and -IgM structure protein antibodies were detected with the iFlash 1800 Chemiluminescence Immunoassay Analyzer (YHLO Biotech, Shenzen, China).

Plasma levels of both remdesivir and its metabolite GS-441524 were determined on day 1, 3 and 5 and were analyzed by liquid chromatography / mass spectrometry as recently described [4]. The precision (accuracy) of remdesivir and GS-441524 spiked quality

Table 1. **Baseline characteristics.**

Parameters	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	65	81	76	64
Sex	Male	Male	Male	Male
BMI (kg/m^2)	29	28	23	20
GFR	>90	>90	77	73
Hospital days before ICU admission (days)	2	5	3	3
Days with symptoms before hospital admission (days)	3	2	5	2
Severity of COVID-19	Severe	Severe	Severe	Severe
Severity of ARDS	Severe	Severe	Severe	Severe
SOFA Score	10	9	11	10
Laboratory parameters (at ICU admission)				
Leukocyte count (G/l)	3.46	4.55	13.71	5.31
C-reactive protein (mg/dl)	9.9	12.8	12.3	8.7
Procalcitonin (ng/ml)	0.1	0.5	0.4	0.4
Interleukin-6 (pg/ml)	31.9	68.6	70.4	57.3
Procedures during ICU stay (Yes/No)				
Mechanical ventilation	Y	Y	Y	Y
Prone positioning	Y	Y	Y	Y
Glucocorticoid (6 mg dexamethasone for 10 days)	Y	Y	Y	Y
Renal replacement therapy	N	N	N	N
Secondary infections during ICU stay	None	Pneumonia related to *Pseudomonas aeruginosa*	Invasive aspergillosis with *Asp. fumigatus*	None
Outcome				
ICU stay (d)	35	16	32	15
death (Y/N)	N	Y	Y	N
Underlying disease	Granulomatosis with polyangiitis	Rheumatoid arthritis	Myasthenia gravis	Kidney transplantation
	Y			Y
Comorbidities (yes/no)				
Arterial hypertension	Y	-	-	Y
DM2	-	N	-	N
Anticoagulation	N		N	
Immunosuppressive medication	Rituximab Prednisolone	Low dose MTX Prednisolone Azathioprin	Mycophenolate mofetil Prednisolone ATG	Tacrolimus Mycophenolate mofetil

BMI, body mass index; ICU, intensive care unit; SOFA score, sequential organ failure score; DM2, diabetes mellitus type 2; MTX, methotrexat; ATG, anti-thymocyte globulin.

control samples in plasma ranged from 4.7% to 6.1% (93.9-101.6%) and from 2.7% to 7.2% (97.6-102.8%), respectively. For statistical analysis SPSS 24.0 (IBM Corp.) was used.

Results and Discussion

Baseline characteristics of the four immunosuppressed critically ill patients are presented in Table 1. Immunosuppressive medication was stopped (or was already stopped before transmission to the ICU) in all patients, except in patient 4, in which a baseline immunosuppressive regime with tacrolimus was continued. Initiation of remdesivir treatment was started in all patients until day 3 after ICU admission. Mean viral load (from BAL) before treatment was 40.92 x 10^7 Geq/ml (day 1 of ICU admission). The mean virus load of 39.74 x 10^7 Geq/ml (±33.25 x 10^7 Geq/ml) on day 1 dropped significantly ($p<0.008$) to 3.54 x 10^6 Geq/ml (±6.93 x 10^6 Geq/ml) on day 3 and to 1.4 x 10^5 Geq/ml (±2.35 x 10^5 Geq/ml) on day 5 of remdesivir treatment. This means a viral load reduction rate of 91.1% between day 1 and 3 and 96% between day 3 and day 5 with a total reduction rate of 99.65% between day 1 and day 5 of remdesivir treatment (Figure 1). The viral load remained constant at a low level until day 14 of the observation.

Seroconversion with detection of IgG antibodies against SARS CoV-2 structure proteins could be detected after 14-25 days after ICU admission in three out of four patients (CLIA IgG levels 40.3-47.24 U/ml). In one patient, anti-SARS-CoV-2-IgG antibodies could be detected upon administration of convalescent plasma which was consecutively given after remdesivir due to flow-cytometric iatrogen B-cell depletion as a consequence of previous rituximab treatment.

We describe the effects of a five-day treatment of remdesivir in four immunocompromised patients with quantitative high SARS-CoV-2 pulmonary viral loads and found a decrease to less than 1% of the initial viral load. After the outbreak of COVID-19 a study using Vero E6 cells showed that remdesivir inhibited the replication of SARS-CoV-2 [5]. These findings could be confirmed in post-exposure experiments of SARS-CoV-2-infected rhesus macaques by inhibiting viral replication [6].

In contrast, Goldberg *et al*. did not find significant reduction rates of viral load in nasal swabs of COVID-19 patients receiving remdesivir treatment [7]. These results are in line with previous results from a macaque experiment, showing that remdesivir did not reduce the viral load in the upper but in the lower respiratory tract which is for the lower respiratory tract in the line with our results [6]. Yet, we cannot exclude that the reductive effect on the viral load may be explained by a T- and B-cell immune response. This delay of detected anti-SARS-CoV-2-IgG and IgM might have been influenced by the type of applicated immunosuppressive medication. We favor a drug effect because of the unique pharmacokinetic properties of remdesivir. When infused it has little blood hydrolysis; most of the drug enters target cells following an enzymatic step of the cell and of the prodrug a phosphorylated S 441 524 which interacts with the RNA which leads to viral blockade. Plasma levels of GS 441 524 are extremely sensitive to small changes in kidney function [4]. In our patients a moderate renal dysfunction led to higher levels of GS 441 524 and these two patients were those who had the highest viral load before therapy. Parent prodrug remdesivir levels of antiviral activity in our patients were far in excess of EC 50 of 47,6 ng/mL, the levels of the GS441524 metabolite in patients 1 and 2 were below to clearly above EC50 of GS441524 of 250,5 ng/mL for patients 3 and 4.

Although the effects of high viral loads on the outcome of affected patients remain unclear to date, clinical and postmortem data in critically ill patients have shown that SARS-CoV-2 viremia leads to a systemic spreading of the viral disease into several other organs beyond the primary affected lungs e.g., to the kidneys or the

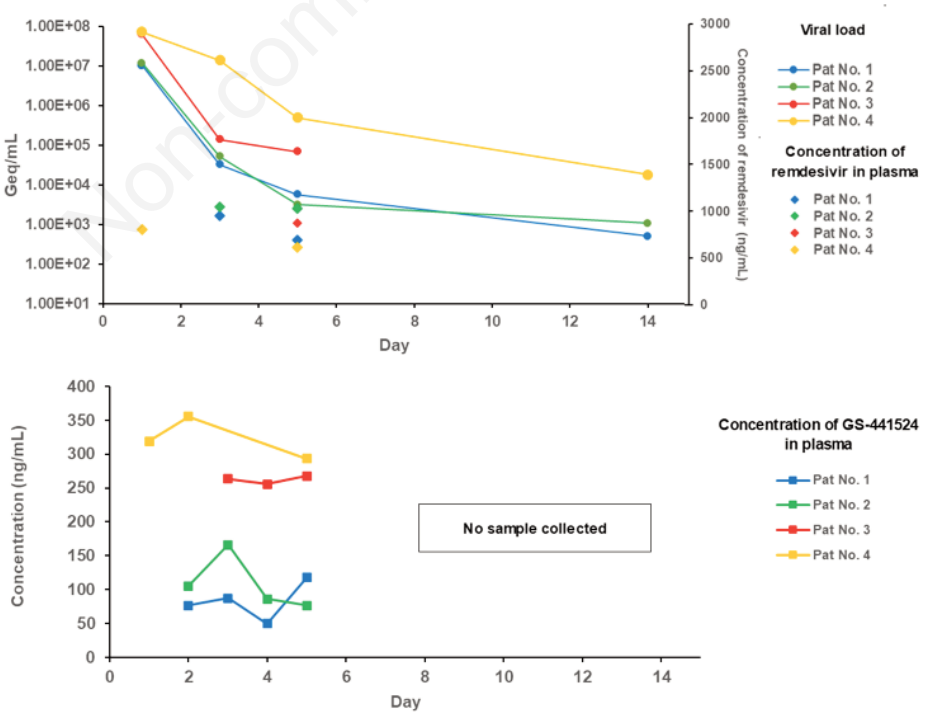

Figure 1. **Viral dynamics during remdesivir treatment and corresponding remdesivir and metabolite plasma levels.**

heart [3]. While these organ complications are commonly reported in critically ill COVID-19 patients, the underlying mechanisms remain unclear and the potential effects of antiviral medication on those observations have not been investigated yet.

Moreover, persistent viral shedding (PSV) is a common event and is associated with immunosuppression, increased IL-6 levels, and the need for mechanical ventilation as known from other viral infections. Treatment with remdesivir potentially reduces SARS-CoV-2 viral load in critically ill immunosuppressed patients: however, the implication of viral load reduction on morbidity and mortality is not very clear, however, new real-life data suggest benefits in patients treated with remdesivir [1,8,9].

Although remdesivir is not recommended for treatment of critically ill COVID-19 patients at the moment, future perspectives of combination therapies with new COVID-19 medications may be interesting and should be investigated.

Conclusion

Our data presents that remdesivir treatment potentially reduces the SARS-CoV-2 viral load in immunosuppressed critically ill patients. However, the implication of viral load reduction on morbidity and mortality needs further investigation.

Abbreviations

BAL: bronchoalveolar lavage;
RT-PCR: real-time polymerase chain reaction;
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

References

1. Dölken L, Stich A, Spinner CD. Remdesivir for early COVID-19 treatment of high-risk individuals prior to or at early disease onset-lessons learned. Viruses 2021;13:963.
2. Tsukagoshi H, Shinoda D, Saito M, Okayama K, Sada M, Kimura H, et al. Relationships between viral load and the clinical course of COVID-19. Viruses 2021;13:304.
3. Fajnzylber J, Regan J, Coxen K, Corry H, Wong C, Rosenthal A, et al. SARS-CoV-2 viral load is associated with increased disease severity and mortality. Nat Commun 2020;11:5493.
4. Sörgel F, Malin JJ, Hagmann H, Kinzig M, Bilal M, Eichenauer DA, et al. Pharmacokinetics of remdesivir in a COVID-19 patient with end-stage renal disease on intermittent haemodialysis. J Antimicrob Chemother 2021;76:825-7.
5. Frediansyah A, Nainu F, Dhama K, Mudatsir M, Harapan H. Remdesivir and its antiviral activity against COVID-19: A systematic review. Clin Epidemiol Glob Health 2021;9:123-7.
6. Williamson BN, Feldmann F, Schwarz B, Meade-White K, Porter DP, Schulz J, et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. Nature 2020;585:273-6.
7. Goldberg E, Ben Zvi H, Sheena L, Sofer S, Krause I, Sklan EH, et al. A real-life setting evaluation of the effect of remdesivir on viral load in COVID-19 patients admitted to a large tertiary centre in Israel. Clin Microbiol Infect 2021;27:917.
8. Chokkalingam A, Li H, Asubonteng J, Mozaffari E, Wang JR, Bush C, et al. Comparative effectiveness of remdesivir treatment in patients hospitalized with COVID-19. World Microbe Forum ASM 2021. Poster 2970. Available from: https://www.askgileadmedical.com/downloads/pdfs/conference-materials/covid-19/asm%202021/ Chokkalingam% 20AP.pdf
9. Buckland MS, Galloway JB, Fhogartaigh CN, Meredith L, ProvineNM, Bloor S, et al. Treatment of COVID-19 with remdesivir in the absence of humoral immunity: a case report. Nat Commun 2020;11:6385.

Received for publication: 9 December 2021. Accepted for publication: 12 April 2022.

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Multidisciplinary Respiratory Medicine 2022; 17:825
doi:10.4081/mrm.2022.825