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Remdesivir retreatment: another unproven intervention for COVID-19

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Remdesivir is approved for the treatment of hospitalized coronavirus disease 2019 (COVID-19) patients.[1] Up to 5%–10% of discharged COVID-19 patients require readmission, most commonly due to worsening respiratory status.[2,3] The treatment of COVID-19 patients readmitted after receiving remdesivir is a challenge and we have observed remdesivir retreatment in such patients, though there is no proof that this practice is beneficial. Available literature is scant as remdesivir retreatment has been reported in only a few individual cases[4–6] and no large studies have been performed or are ongoing to the best of our knowledge. This practice is also unaddressed in current treatment guidelines.[7,8]

To shed light on the practice of remdesivir retreatment and encourage an evidence-based approach, we collected retrospective data on readmitted COVID-19 patients from a single healthcare system in Chicago. Our findings illustrate the lack of a standardized approach, underscoring the need for structured studies and treatment guidelines. Specifically, we identified 13 patients with two separate admissions during which at least two doses of remdesivir were administered between June 2020 and February 2021 (Table 1). All had a positive SARS-CoV-2 PCR test at the time of readmission. The patients (eight men and five women) were between 32 and 92 years old. Eight of them had immunocompromising diagnoses of transplantation, malignancy receiving chemotherapy or current immunotherapy. Eight of these patients completed a 5 day course of remdesivir retreatment, while five patients were retreated with remdesivir for only 2 days prior to their discharge or death. Assessment of clinical notes revealed substantial subjectivity in the decision to retreat with remdesivir. Notably, the rationale provided fell into three categories: persistent symptoms, worsening respiratory status and/or 'high-risk patient'. High risk was not clearly or uniformly defined. In only three of the cases did physicians use low cycle threshold (Ct) measurements (16–21, corresponding to relatively high viral load) to justify retreatment; Ct values were not consistently reported to clinicians during the period. Finally, there was substantial heterogeneity in the outcomes observed, as can be expected in a population with divergent underlying medical conditions and COVID-19 disease severity. After retreatment, eight patients were discharged; five on room air and three on supplemental oxygen. In-hospital all-cause mortality rate was 5/13 (38%), being 4/8 (50%) in the immunocompromised group and 1/5 (20%) in the non-immunocompromised group.

This retrospective descriptive study highlights the need to determine whether remdesivir retreatment improves outcomes since the landscape of COVID-19 treatment is littered with interventions that were presumed effective and hence widely adopted, only to fall short under careful research scrutiny.[9] In this light, remdesivir retreatment should be considered an unproven intervention unless studies indicate otherwise. Remdesivir works by inhibiting SARS-CoV-2 replication through its effect on RNA-dependent RNA polymerase.[10] As such, it is most likely to be effective in the early stages of COVID-19 when viral replication is high, as opposed to later in the course when the secondary hyperactive immune response may be the dominant driver of injury. This is supported by the results of ACTT-1 where the largest effect size was recorded among patients requiring supplemental oxygen, but not mechanical ventilation.[10] Moreover, the clinical impact of remdesivir has been limited in trials to date. In the landmark ACTT-1 study, this drug shortened time to recovery in hospitalized patients with COVID-19 not requiring mechanical ventilation,[10] but had no significant effect on mortality, though the study was underpowered for the mortality endpoint. An adequately powered study (Solidarity) showed no significant effect on mortality.[11]

We opine that the immunocompromised population deserves special attention in studies of remdesivir retreatment since SARS-CoV-2 detection tends to persist longer in this subpopulation. Indeed, detection of SARS-CoV-2 by PCR may continue for several months post-infection in immunocompromised patients, whereas virus remains detectable for approximately 2 weeks in the upper respiratory tract of the general population.[5] A critical question is whether detected viral RNA represents shedding of non-replicating virus versus ongoing viral replication as only the latter is expected to be clinically consequential. Evaluation of Ct values is one way to separate these scenarios.[12–14] This is relevant because evidence of prolonged viral replication in a population may theoretically extend the window during which pharmacological inhibition of viral replication with remdesivir may be advantageous. Meanwhile, anecdotal reports of remdesivir retreatment in immunocompromised patients who had evidence of ongoing viral replication (low Ct values) have shown mixed outcomes with some, not all, patients experiencing temporal improvements in symptoms and/or markers of inflammation.[4–6] There were eight immunocompromised patients in

Table 1. Patients retreated with remdesivir

Comorbidities	Age (years)	Gender	Remdesivir treatment	Days of therapy	Days between treatment	Room air saturation at admission (%)	Maximal oxygen requirement	Days of steroid therapy	Hospitalization outcomes
Non-immunosuppressed									
asthma, CAD, CKD, HTN	92	male	initial	5	9	93	2 L	10	discharged on RA
			retreatment	5		86	5 L	5	
CAD, CHF, COPD, DM, DVT, HL, iron deficiency anaemia, obesity, TIA	77	female	initial	5	14	87	3 L	5	discharged on RA
			retreatment	5		94	2 L	10	
Angelman syndrome, chronic aspiration, chronic hypoxic respiratory failure (on oxygen at night), obesity, seizures	40	male	initial	5	10	84	4 L	10	discharged on oxygen
			retreatment	2		88	6 L	5	
DM, HTN, hypothyroidism, NHL in remission	55	female	initial	5	106	92	3 L	0	discharged on RA
			retreatment	3	139	89	RA	1	
			retreatment[a]	5		90	3 L	6[b]	
CHF, COPD on oxygen, CVA, DM, DVT/PE, HTN, NSTEMI	72	female	initial	5	27	100	MV	8	deceased
			retreatment	2		99	MV	2	
Immunosuppressed									
bullous pemphigoid on rituximab, CKD, COPD, DM	62	male	initial	3	16	92	2 L	10	discharged home on RA
			retreatment	5		85	HFNC	10[b]	
BOLT, ILD	32	female	initial	10	10	88	2 L	0[c]	discharged home on oxygen
			retreatment	2		90	1 L	0[c]	
CKD, metastatic colon cancer	48	male	initial	5	15	98	RA	0	deceased
			retreatment	2		100	3 L	0	
follicular lymphoma	49	male	initial	5	49	97	4 L	14	discharged home on oxygen
			retreatment	5		98	MV	taper for new HLH	
lymphoma, DVT	72	female	initial	2	36	94	RA	2	deceased
			retreatment	5		70	4 L	5	
AML, fungal pneumonia, *Staphylococcus epidermidis* endocarditis	40	male	initial	5	9	89	4 L	11	deceased
			retreatment	5		MV	MV	11	
kidney transplant	53	male	initial	4	15	85	3 L	4	deceased
			retreatment	2		50	MV	10	
atrial fibrillation, NHL on rituximab, CKD, HTN	84	male	initial	3	20	90	RA	0	discharged on RA
			retreatment	5		88	3 L	5	

BOLT, bilateral orthotopic lung transplantation; CAD, coronary artery disease; CHF, chronic heart failure; CKD, chronic kidney disease; CVA, cerebrovascular accident; DM, diabetes mellitus; DVT, deep-vein thrombosis; HFNC, high-flow nasal cannula; HL, hyperlipidaemia; HLH, haemophagocytic lymphohistiocytosis; HTN, hypertension; ILD, interstitial lung disease; MV, mechanical ventilation; NHL, non-Hodgkin's lymphoma; NSTEMI, non-ST-elevation myocardial infarction; PE, pulmonary embolism; RA, room air; TIA, transient ischaemic attack.

[a]Patient received third treatment of remdesivir.

[b]Patient received prednisone taper after initial steroid treatment.

[c]Patient was on chronic prednisone due to recent transplant status.

our study, a number too small to draw conclusions on the effects of remdesivir retreatment in them.

In summary, we herein draw attention to the practice of remdesivir retreatment in readmitted COVID-19 patients. Research is needed to determine whether this practice is beneficial and whether potential effects vary based on the patient's immune status.

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Transparency declarations

None to declare.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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