A Randomized Control Trial of Ravulizumab for Treatment of Patients With COVID-19 Infection and Kidney Injury

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INTRODUCTION

Patients affected by severe COVID-19 infection often develop end-organ damage that manifests as acute kidney injury (AKI).[1,2] It has been reported that greater than 20% of such patients are diagnosed with AKI, but the long term impact on future prevalence of chronic kidney disease has yet to be rigorously quantitated.[3] There is substantial evidence that primary events of AKI in this circumstance occur on the luminal surface of the endothelial cell in the microvasculature of the kidney,[4-7] including histopathological descriptions of kidney-specific endothelitis and glomerular fibrin thrombi.[8] These findings can be explained in part by complement pathway activation resulting in endothelial injury and kidney-specific thrombotic microangiopathy.[9,S1] Prevalence of kidney-specific thrombotic microangiopathy reported in case series is 4% to 42%.[S2-S4] Complement deposition localized to the endothelial cell in the kidney is a common cause of thrombotic microangiopathy[S5] and may describe the mechanism of kidney-specific thrombotic microangiopathy in COVID-19 infection. C1q and lectin pathways have been implicated due to enhanced C4b binding to the surface of kidney endothelium in select patients.[S6] Because therapy that inhibits viral replication is limited in patients with kidney injury due to the exclusion of these patients from clinical trials,[S7] complement pathway activation and subsequent endothelial injury in patients with reduced estimated glomerular filtration rate may be perpetuated when optimal therapy cannot be offered.

Ravulizumab is a humanized monoclonal antibody that binds an epitope on the complement component 5 protein (C5) and inhibits the cleavage of C5 into C5a and C5b on the endothelial cell surface, thus preventing endothelial dysfunction.[S8] Ravulizumab ameliorates the pathophysiological sequalae which develop from uncontrolled complement activation. It is utilized for the treatment of atypical hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria in all stages of chronic kidney disease.[S9,S10] In this study, we report the use of ravulizumab to treat complement cascade over-activation in patients with AKI in the setting of COVID-19 infection with focus on a primary follow-up period of 30 days.

RESULTS

Patients were screened between January 1, 2021 and July 30, 2021. A total of 43,093 patients were evaluated in the study site's emergency department during the enrollment period (Supplementary Figure S1A). During the same time period, 1056 new cases of COVID-19 infection were diagnosed (Supplementary Figure S1B). A total of 114 patients (10.8% of admitted) met the criteria for enrollment (Supplementary Figure S1C). Thirteen (11.4% of screened) patients identified to have

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Table 1. Enrollment and treatment parameters in patients diagnosed with COVID-19 associated AKI

Age (yr)	Weight (kg)	SOT	C19 PTE (yr)	WHO OE	GFR (ml/min/1.73 m²) PTE (d)	Rav (g)	Adm (d) PTE (d)	DC (d) AE (d)	LC (d)
SOC+R									
65	66.7	H	8	3	23	2.7	8	2	332
68	115.7		5	4	14	3	5	12	342
28	73.5		42	2	11	2.7	14	4	311
27	130.7		12	2	10	3	12	1	256
51	90.8	K	17	4	32	2.7	4	11	279
63	88.5		57	2	9	2.7	1	1	220
50±18	94.3±24.6		23±21	3±1	16±8	2.8±15	7±5	5±5	290±47
SOC									
65	64.4		4	2	28		4	2	310
73	108.2		8	4	21		14	8	8
36	62.6		11	4	16		11	26	273
62	111		32	4	12		7	21	22
55	83.9		11	2	17		3	13	276
64	72.9		22	1	25		4	10	256
45	98.9	L	4	4	21		2	5	5
57±12	85.9±20.3		13±10	3±1	20±5		6±4	12±8	164±133

Adm, most recent admission; AE, after enrollment; C19, SARS-CoV-2 infection; DC, discharge; GFR, estimated glomerular filtration rate; H, heart; K, kidney; LC, last contact after enrollment; L, lung; OE, on enrollment; PTE, prior to enrollment; Rav, ravulizumab; SOC, standard of care; SOC+R, standard of care plus ravulizumab; SOT, solid organ transplant; WHO, World Health Organization score.

COVID-19 infection were enrolled in the study (Table 1, Supplementary Table S1), including 4 patients with solid organ transplants (Table 1, Supplementary Table S1). Six patients were randomized to receive ravulizumab in addition to standard of care (SOC+R) and 7 patients were randomized to SOC.

Patients were enrolled 23±21 days (SOC+R) and 18±10 days (SOC) following the initial positive SARS-CoV-2 screening test (Table 1). Mean number of hospital days before enrollment was 7±5 days (SOC+R) versus 6±4 days (SOC). Three patients randomized to the SOC group died after enrollment. Deaths occurred on days 5, 8, and 22. Cause of death included pneumonia, acute respiratory distress syndrome, and cardiac arrest, respectively. Two of 4 participants with a functioning solid organ transplants died. No participant with a solid organ transplants in the SOC+R died. Thirty days after enrollment, mean number of hospital-free days was 290±47 days (SOC+R) versus 164±144 days (SOC), respectively (Table 1).

Mean dose of ravulizumab infused in the SOC+R was 2800±155 mg (Table 1). Thirty-day mean area under the curve was 1341±835 μg/ml per day (Figure 1a). Free C5 levels increased over time following ravulizumab infusion and corresponded with decreasing ravulizumab blood levels over the same time interval (Figure 1b) ($P <$ 0.001). Ravulizumab blood levels and free C5 levels corresponded with decreased soluble intercellular adhesion molecule 1 blood levels, decreased soluble c5b-9 levels (Figure 1b), and increased mean platelet count (Figure 1c [i]). SOC mean platelet count decreased

by 29.6% after 30 days (Figure 1c [ii]). Mean platelet count increased by 36.1% in the SOC+R over the 30-day period immediately following infusion ($P = 0.001$). During this same time period, there was a decreased number of anuric days observed in the SOC+R (Figure 1d [i]) compared to SOC (Figure 1d [ii]) ($P = 0.009$). Mean hemoglobin at enrollment was 9.3±1.6 (SOC+R) (Supplementary Figure S2A [i]) vs. 9.4±2.2 g/dl (SOC) (Supplementary Figure S2A [ii]), which decreased in both groups after 30 days (7.8±1.5 vs. 8.1±1.7 g/dl, respectively). Schistocytes were detected proximate to enrollment but infrequently (Supplementary Figure S2A [i],[ii]). Mean white blood cell counts were also stable in both groups for 30 days after enrollment (Supplementary Figure S2B[i],[ii]), however the absolute lymphocyte count increased in the SOC+R from 0.89±0.2 to 3.72±0.3 x 10^3/μl (Supplementary Figure S2C [i] vs. S2C [ii], respectively) ($P = 0.008$) while the absolute neutrophil count increased in the SOC over the same time period from 9.6±3.7 to 11.7±4.6 x 10^3/ μl (Supplementary Figure S2D[ii] vs. S2D[ii], respectively) ($P = 0.02$). Lactate dehydrogenase decreased in both groups over time (Supplementary Figure S2E [i],[ii]).

All patients were diagnosed with kidney injury with a mean estimated glomerular filtration rate of 16±8 (SOC+R) versus 20±5 ml/min per 1.73 m² (SOC) at enrollment (Table 1, Supplementary Figure S3A [i],[ii]). Accounting for 2 patient deaths, mean estimated glomerular filtration rate 30 days following enrollment was similar between the SOC+R and SOC groups (23±8 vs. 17±10 ml/min per 1.73 m², respectively),
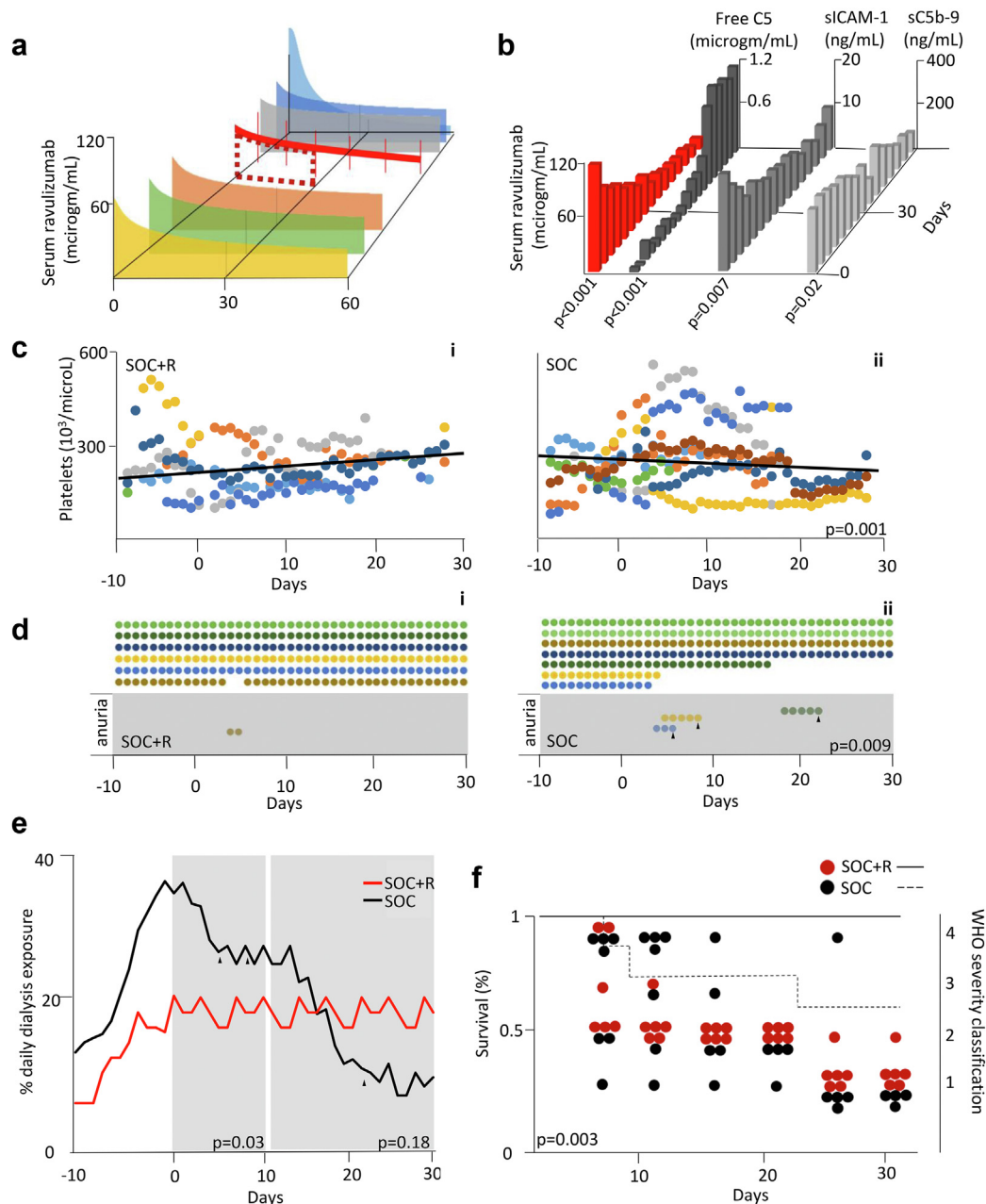
Figure 1. Ravulizumab treatment measures in patients diagnosed with COVID-19-Associated AKI. (a) Serum ravulizumab levels in 6 enrolled patients, mean value over 60 days (solid red line), and mean 30-day area under the curve [circumscribed red dotted line] after enrollment, (b) Free C5 serum levels in 6 enrolled patients with corresponding serum ravulizumab levels, soluble ICAM-1, and soluble C5b-9 levels, (c) Platelet counts in patients receiving [i] standard of care and ravulizumab (SOC+R) compared to [ii] SOC alone for 30 days after enrollment, (d) Days of anuria in [i] SOC+R and [ii] SOC for 30 days after enrollment [black arrow = patient death], (e) 5-day mean daily dialysis frequency in SOC+R (red) vs. SOC (black) after enrollment (arrows = patient death), (f) Serial World Health Organization severity classification SOC+R (red) vs. SOC (black) and corresponding Kaplan Meier survival curve (SOC+R = solid line, SOC = dotted line). C5, component 5 protein; ICAM-1, intercellular adhesion molecule 1; SOC, standard of care.

(Supplementary Figure S3A [i], [ii]). The estimated glomerular filtration rate trend over 30 days in the SOC+R increased compared to SOC ($P = 0.009$) although this trend incorporated several nonanuric patients supported by hemodialysis. This trend also corresponded with a reduced frequency of dialysis events in the SOC+R for 10 days after enrollment (Figure 1e) ($P = 0.03$). Nevertheless. at day 30, exposure to hemodialysis in the SOC+R survivors was increased compared to SOC survivors (18% vs. 9%, respectively). One patient in each study arm requiring extended hemodialytic support was subsequently discontinued from maintenance hemodialysis within 120 days.

World Health Organization severity classification score was 3±1 (SOC) and 3±1 (SOC+R) after enrollment and decreased in the SOC+R compared to the SOC after 30 days (Figure 1f) ($P = 0.003$). AKI score between groups was 3±1 versus 3±1 at enrollment and was maintained in SOC+R after 30 days compared to SOC (3±1 vs. 2±1, respectively) ($P = 0.01$) (Supplementary Figure S3B). Elevated AKI scores in SOC+R paralleled high cumulative hemodialysis exposure 30 days after enrollment.

DISCUSSION

In this pilot study we demonstrated that a mean dose of 2800 mg of ravulizumab given in the setting of COVID-19 infection and AKI was associated with an increased platelet count and reduced number of anuric days in patients frequently requiring acute hemodialysis. When coupled with decreasing soluble intercellular adhesion molecule 1 and C5b-9 levels in participants receiving ravulizumab, a mechanism for endothelial cell membrane stabilization in the kidney could be inferred. These results occurred during a 30-day period when ravulizumab blood levels were detected in all treated patients and corresponded with a clinically significant depression in circulating free C5 levels. Such findings were consistent with therapeutic complement cascade inhibition[S11] for a time interval anticipated by the FcRn-mediated antibody recycling properties of ravulizumab.[S8] Although mortality preceded by anuria was decreased in the SOC+R group during the same time period, the medical complexity of each participant precluded a strong association between ravulizumab treatment and improved survival. This initial report warrants further study in a larger group where multivariate models can be employed.

To summarize, the optimal treatment regimen for kidney injury associated with COVID-19 infection continues to be refined. Due to the recurrent impact of COVID-19 infection on patients throughout the world, targeted therapies for concomitant kidney injury merit future investigations in order to reduce incidence of AKI and potentially reduce future prevalence of chronic kidney disease.

DISCLOSURE

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplemental Methods.

Supplemental Results.

Supplemental References.

Figure S1. Frequency of patients diagnosed with COVID-19 infection in a tertiary care hospital where patients were then enrolled.

Figure S2. Laboratory parameters for the 30 day period following participant enrollment.

Figure S3. Kidney function and injury levels for the 30 day period following participant enrollment.

Table S1. Patient characteristics.

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