Management of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis with COVID-19: A Single Center Experience

Abstract

Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) patients particularly presenting as rapidly progressive glomerulonephritis (RPGN) are at extremely high risk of progressing to end-stage kidney disease (ESKD); therefore, timely intervention is important. We describe our experience of managing six AAV patients who were on treatment (induction phase) and developed COVID-19. Cyclophosphamide was stopped till RT-PCR for SARS-CoV-2 was reported negative and patient had improved symptomatically. Out of our six patients, one died. Subsequently, cyclophosphamide was successfully resumed in all the surviving patients. In patients of AAV with COVID-19, close monitoring and withholding of cytotoxic medication and continuing steroids till active infection subsides is an effective treatment strategy until more and more data from well-conducted largescale studies become available for guidance.

Keywords: *AAV, ANCA, COVID-19, cyclophosphamide*

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Introduction

As the pandemic of coronavirus disease 2019 (COVID-19) continues to rage, it is creating more and more challenges for the healthcare fraternity to deal with the complex interplay of disease processes. As COVID-19 situation continues to unfold, the guidance for management of COVID-19 and its ramifications on other disease management is derived from experiences from different centers across the globe. COVID-19-related clinical practice continues to be updated with respect to various kidney diseases, dialysis and kidney transplantation.[1–3] Remdesivir, among other medications, has emerged as a potential candidate for the management of COVID-19. As remdesivir has low water solubility, sulfobutylether-β-cyclodextrin (SBECD) is added to it. SBECD is dialyzable and hence can be used in patients with renal failure and subsequently removed using renal replacement therapy (RRT).[4,5] The temporal relation of ANCA vasculitis with COVID-19 observed includes pre-infection, during infection and following infection. Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) patients particularly presenting as rapidly progressive glomerulonephritis (RPGN) are at extremely high risk of progressing to end-stage kidney disease (ESKD) and therefore timely intervention cannot be overemphasized.[6] The guidance on management of AAV patients on immunosuppression (induction phase in particular) who develop COVID-19 remains largely based on case reports and small case series.[1,3,4,7–9] We describe our experience of managing AAV patients who were on treatment (induction phase) and developed COVID-19.

Case Series

The age range of our series was 36–76 years with 3 males and 3 females [Tables 1 and 2]. All of our patients were on cyclophosphamide and steroids as part of induction therapy, and two of them had received plasmapheresis previously; none of our patient had received rituximab as induction agent. Four of our patients required oxygen support and two did not require any oxygen support. One patient with anti-PR3 AAV, who had received methylprednisolone 500 mg daily for 3 days and cyclophosphamide pulse 10 days prior to COVID-19, expired. This patient had been severely hypoxemic, had leucopenia and required mechanical

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Table 1: Patient summary prior to developing COVID-19

Patient No.	Summary
1	A 37-year-old female was diagnosed with myeloperoxidase (MPO)-AAV with pulmonary and kidney involvement and had received plasmapheresis and two doses of intravenous (IV) cyclophosphamide; last dose had been received three weeks prior. Patient, while on oral steroids and Bactrim prophylaxis, developed severe COVID-19 and was managed with IV steroids, remdesivir, RRT support, and anticoagulation, and improved in hospital.
2	Anti-PR3 AAV patient aged 36 years, who had previously presented with sinusitis and renal involvement and had been started on oral cyclophosphamide two weeks prior along with Bactrim prophylaxis and oral steroids, developed COVID-19, requiring hospitalization. Patient was managed with IV steroids, supplemental oxygen, and anticoagulation. Patient did not require RRT and was discharged after stabilization.
3	Patient with anti-PR3 AAV, who had previously presented with hemoptysis and anemia along with renal impairment and had been started on oral cyclophosphamide four weeks before developing COVID-19, was managed with supplemental oxygen, IV steroids, and anticoagulation.
4	Elderly female had presented two weeks ago with RPGN, nasal crusting and hemoptysis, and had been given steroids and IV cyclophosphamide pulse 10 days before developing COVID-19. Patient was also on sulfamethoxazole-trimethoprim prophylaxis. She required mechanical ventilation and was given IV steroids and antibiotics along with anticoagulation. Patient died in hospital.
5	A 54-year-old male patient had presented previously with RPGN and had been started on oral cyclophosphamide and steroids along with Bactrim prophylaxis. Patient had MPO-AAV and was hospitalized with COVID-19. Patient stabilized but continued to be dialysis dependent on hospital discharge.
6	Elderly female was diagnosed with MPO-AAV, had previously received plasmapheresis and two IV cyclophosphamide pulses and had been on Bactrim prophylaxis. This patient had RPGN, and pulmonary involvement and had received last IV cyclophosphamide pulse 15 days prior to COVID-19 infection. Patient required RRT during hospital stay and was dialysis independent at the time of hospital discharge.

ventilation. She received remdesivir, antibiotics, anticoagulation and expired on day 5 of hospitalization. In the rest of the patients, cyclophosphamide was stopped till RT-PCR result was negative and patient had improved symptomatically. All of our surviving patients were RT-PCR negative at hospital discharge. Subsequently, cyclophosphamide was successfully resumed in all of the surviving patients [Table 2]. We observed that interruption of cytotoxic agent and continuing steroids along with other measures, particularly anticoagulation, are viable options in the management of this complex situation.

Discussion

As immunosuppression puts patients at increased risk of COVID-19 infection and complications thereof, a careful balance between the intensity of immunosuppression (needed for active renal or systemic disease) and COVID-19 severity is needed. The management guidance regarding COVID-19 per se and the underlying renal diseases like lupus, glomerulonephritis, and vasculitis continues to evolve as more and more data accumulates. So far, the evidence is based on smaller studies and case series. In a case series by Nupur N. Uppal *et al*.,[10] two patients with COVID-19 and Pauci-immune glomerulonephritis (GN) were managed with steroids and rituximab and both patients improved. In another study, two patients were reported by Tugba Izci Duran *et al*.[11] who had developed AAV following COVID-19 and were managed with IVMP/CYC and with plasmapheresis in one patient who continues to be dialysis dependent. Sam Kant *et al*.[8] suggested that induction immunosuppressive agents can be employed shortly after improvement of acute COVID-19 presentation to treat AAV. Our study too suggests that immunosuppressive agents can be resumed as soon as COVID-19 settles. Sam Kant *et al*.,[9] in another study, concluded that the incidence of COVID-19 in patients with AAV is similar to that of the general population and that the care of AAV patients has been affected by the ongoing pandemic. They suggested that reduction of immunosuppression may not be needed or may prove detrimental because of the risk of AAV relapse. We suggest that in patients on AAV induction contracting COVID-19, withholding cytotoxic agent and close monitoring till infection settles is a pragmatic course to take. International Registry of COVID infection in glomerulonephritis (IRoc-GN) compared 40 patients with glomerulonephritis and COVID-19 to 80 COVID-positive control cases without glomerulonephritis and found that patients with GN had higher mortality (15%) compared to patients without GN (5%). Similarly, acute kidney injury (AKI) was higher in the GN group (39% vs 14% respectively), and therefore patients with GN and COVID-19 must be monitored closely, particularly when patients have hypoalbuminemia.[7] In a recent study that included 16 patients with COVID-19 who were on AAV induction treatment, it was found that seven (44%) of these patients required hospitalization and four patients died.[12] In our study, five of the six patients (83.3%) required hospitalization and one patient (16.6%) died. Table 3 shows a comparison of our study with the other studies.

Conclusion

In patients of AAV with COVID-19, close monitoring and withholding cytotoxic medication and continuation of steroids till active infection subsides is an effective

Table 2: Clinical and demographic characteristics, and management strategies

Patient	Age/ Sex	ANCA type	Immunosuppression	Oxygen support	Baseline creatinine (mg/dl)	Peak creatinine during COVID-19	Hospital stay (days)	CT chest severity score	Serum creatinine at discharge (mg/dl)	COVID-19 management	Immunosuppresion resumed	Outcome
1	37/F	MPO-AAV, diagnosed 5 weeks prior	Prednisolone 30 mg, IV cyclophosphamide pulse 3 weeks prior, plasmapheresis 10 sessions	Non - invasive ventilation	3.4	9.5	14	17/25	2.9	Remdesivir, enoxaparin, cyclophosphamide pulse delayed, IV dexamethasone 6 mg during hospital stay	2 weeks after hospital discharge	Improved
2	36/M	Anti - proteinase-3	Prednisolone 40 mg, Oral cyclophosphamide 2 mg/kg	Nasal prongs	3.1	3.9	13	15/25	3.0	Enoxaparin, cyclophosphamide withheld, IV methylprednisolone 60 mg twice daily for 1 week followed by oral prednisolone 40 mg daily	1 week after hospital discharge	Improved
3	62/M	Anti - proteinase-3	Prednisolone 25 mg, oral cyclophosphamide 1 mg/kg	Nasal prongs	2.6	3.5	4	12/25	2.7	Enoxaparin, azithromycin, cyclophosphamide withheld, IV dexamethasone 6 mg daily	10 days after hospital discharge	Improved
4	70/F	Anti - proteinase-3	Prednisolone 40 mg, IV Cyclophosphamide pulse 10 days prior	Mechanical ventilation	4.5	4.8	5	19/25	-	Remdesivir, enoxaparin, levofloxacin, IV dexamethasone 6 mg daily	-	Died
5	54/M	MPO-AAV	Prednisolone 20 mg, oral cyclophosphamide 2 mg/kg for 1 month	None	4.7	6	Nil	Not done	5.1	Symptomatic treatment, cyclophosphamide withheld, oral prednisolone 40 mg daily during hospital stay	1 week after hospital discharge	Dialysis dependent
6	76/F	MPO-AAV	Prednisolone 30 mg, IV cyclophosphamide 700 mg 2 pulses, Plasmapheresis 8 sessions	None	4.5	9.4	10	Not done	4.2	Symptomatic treatment, cyclophosphamide withheld, oral prednisolone continued as such	2 weeks after hospital discharge	Dialysis independent

Abbreviations: IV, Intravenous; M, Male; F, female; MPO, Myeloperoxidase; ANCA, Antineutrophil cytoplasmic antibody

Table 3: Comparison of our study with other studies

	Kant S *et al*.[8]	Uppal NN *et al*.[10]	Izci Duran T *et al*.[11]	Present study
n	6	2	2	6
AAV type (n)	MPO (1) Anti-PR3 (5)	MPO (1) Anti-PR3 (1)	MPO (1) Anti-PR3 (1)	MPO (3) Anti-PR3 (3)
Induction agent (n)	Cyclophosphamide (6) Rituximab (2) Plasmapheresis (2)	Rituximab (2)	Cyclophosphamide/ plasmapheresis (1) Cyclophosphamide (1)	Cyclophosphamide (4) Cyclophosphamide/ plasmapheresis (2)
COVID-19 management	Remdesivir (4) Plasma (1)	Tocilizumab/convalescent plasma (1) HCQ/azithromycin (1)	Favipiravir (2)	Remdesivir (2) Withholding cyclophosphamide (6)
Outcome	Recovered (5) Prolonged hospitalization (1)	Recovered	Dialysis dependent (1) Improved (1)	Recovered (5)
Deaths	-	-	-	1

treatment strategy till more and more data from well-conducted largescale studies becomes available for guidance.

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Conflicts of interest

There are no conflicts of interest.

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