The coronavirus disease 2019 (COVID-19) pandemic has not only stressed medical systems with its acute presentations but also conferred an additional permutation to the management of various established diseases. This includes patients with autoimmune disease requiring immunosuppression. The optimal management of immunosuppression during the pandemic and in those with acute infection still remains a matter of debate. We recently reported significant disruption on the chronic care of patients with antineutrophil cytoplasmic antibody–associated vasculitis (AAV) as a result of the pandemic, with a sizeable proportion of patients having their immunosuppression held and that the risk of disease relapse likely far outweighs the risk of COVID-19.1 Also, with the use of protective equipment and adherence to social isolation restrictions, the incidence of COVID-19 in patients with AAV may be similar to that of the general population. The characteristics and outcomes of COVID-19 in patients with new and established diagnoses of antineutrophil cytoplasmic antibody–associated vasculitis (AAV) as a result of the pandemic, with a sizeable proportion of patients having their immunosuppression held and that the risk of disease relapse likely far outweighs the risk of COVID-19.

RESULTS

Four cases of AAV diagnosed at the time of acute presentation of COVID-19, along with 8 cases of patients with a pre-existing diagnosis of AAV, have been reported in the literature (in addition, we report 6 cases with established AAV from our institution; n=14). With respect to the patients newly diagnosed with AAV (n=4), the median age was 41 years, with male and proteinase 3 antibody predominance (Table 1). All patients had evidence of acute kidney injury (median creatinine 5.5 mg/dl) with evidence of crescentic necrotizing glomerulonephritis on kidney biopsy. All patients received pulse steroids, with concomitant rituximab (RTX) administration in two, and cyclophosphamide administration. Two patients with severe alveolar hemorrhage required plasmapheresis, with 1 patient dying (this patient did not receive immunosuppression). The remaining 3 patients who received immunosuppression for AAV demonstrated evidence of clinical recovery.

In patients with established AAV presenting with COVID-19 (n=14), the median age was 54 years, with equal gender distribution and proteinase 3 predominance (n=12). Duration of antineutrophil cytoplasmic antibody diagnosis had a disparate range of 0.5–396 months (Table 2). Majority of patients (11 of 14) were on RTX and oral prednisone for maintenance therapy, with the median duration elapsed since last administration of RTX being 60 days. All patients had evidence of bilateral interstitial and ground-glass opacities on lung radiology, with only 1 patient requiring mechanical ventilation. Thirteen of 14 patients are in
sustained clinical recovery, with 1 currently hospitalized with a positive clinical trajectory.

**DISCUSSION**

This combined case series review brings forward some pertinent aspects of the characteristics and outcomes of patients with newly diagnosed and established AAV diagnosis in the setting of COVID-19 infection. It is unknown if SARS-CoV-2 triggers autoimmunity. The emergence of pediatric multisystem inflammatory disease in temporal relation to SARS-CoV-2 infection is an example of SARS-CoV-2 triggering vasculitis. In the newly diagnosed patient, the predomiance of proteinase 3 provides further evidence for infectious antigen stimulation leading to generation of autoimmunity, especially in the setting of proteinase 3 AAV. Additionally, both COVID-19 and AAV are associated with formation of neutrophil extracellular traps, providing further plausible mechanisms involved in the development of autoimmunity in the setting of the acute viral infection.

Most importantly, these cases have provided possible strategies for management of immunosuppression at the time of a pandemic, where constant uncertainty regarding the same exists. In patients with a new diagnosis of AAV, treatment with pulse steroids with either RTX or cyclophosphamide shortly after acute presentation of COVID-19 led to overall sustained clinical recovery, with no worsening or recurrence of manifestations of infection. With respect to established AAV cases, the median duration elapsed since RTX administration was 60 days. Not only did all of these patients recover, but also only 1 on RTX maintenance required mechanical ventilation. This is in keeping with proposed theories that RTX may limit cytokine storm and prevent further worsening of clinical status. Similar experience has been reported in patients receiving B cell–depleting therapies in diseases such as multiple sclerosis and pemphigus vulgaris, along with patients with other autoimmune diseases on biologic therapies. The only caveat is to recognize that patients previously treated with RTX may demonstrate prolonged viral shedding devoid of any symptoms. This may influence recommendations for duration of quarantine for this population of patients so as to prevent inadvertent exposure to other individuals.

In conclusion, the use of immunosuppression in patients with COVID-19 in the setting of new and established diagnoses of AAV may not be associated with deleterious outcomes. Induction immunosuppression could be used shortly after improvement of acute COVID-19 presentation to treat newly diagnosed AAV. On the other hand, maintenance immunosuppression has the potential to attenuate the severe inflammatory effects of COVID-19 and may not be associated with worse outcomes.

**DISCLOSURE**

DG reports being consultant to ChemoCentryx and Aurinia. All the other authors declared no competing interests.
| Case report | Age | Gender | Ethnicity | Peak creatinine (mg/dl) | Duration of ANCA diagnosis (mo) | ANCA type | Lung radiology | ANCA maintenance | Last IS to COVID diagnosis (d) | Respiratory failure | COVID-19 treatment | COVID-19 outcome | Comments |
|-------------|-----|--------|-----------|-------------------------|-------------------------------|-----------|----------------|------------------|--------------------------|----------------|-------------------|----------------|---------|
| Guilpain2   | 52  | F      | NR        | NR                      | 396                           | PR3       | Bilateral interstitial pneumonia | RTX              | 1            | No               | MV               | Lopinavir/ritonavir; HCQ | Recovered from respiratory failure; discharged on day 29 of admission | Received RTX a day prior to COVID presentation |
| Sharmeen63  | 27  | F      | Hispanic  | NR                      | 1                             | PR3       | Bilateral multifocal opacities    | RTX, prednisone (20 mg) | 60           | No               | NRB, 15 L          | HQC, tocilizumab    | Recovered          | On 20 mg prednisone at the time of COVID diagnosis |
| Schramm66   | 25  | M      | NR        | NR                      | 2                             | PR3       | Bilateral GGOs                    | RTX, CYC (induction), prednisone (60 mg) | 9             | No               | Low-flow, 2 L       | HQC, lopinavir/ritonavir | Recovered          | Nosocomial infection Ongoing 60 mg prednisone, 9 d after last of 5 cyclophosphamide infusions and 19 d after the last of 4 rituximab infusions |
| Daniel3     | 55  | M      | NR        | NR                      | 324                           | PR3       | Bilateral GGOs (80% involvement)  | RTX, prednisone (4 mg) | 120           | No               | None              | HQC, azithromycin, lopinavir/ritonavir | Recovered, discharged home after 23 d | On 4 mg prednisone at the time of diagnosis |
| Leipe59     | 63  | M      | NR        | 3.4                     | 72                            | PR3       | Bilateral GGOs                    | RTX, prednisone (5 mg) | 14            | No               | Face mask, 6 L      | None              | Readmitted with worsening respiratory symptoms on day 14; eventual recovery | On 5 mg prednisone at the time of diagnosis |
| Shenavandeh10 | 35  | M      | NR        | 72                      | PR3                           | Multiple new left-sided peripheral GGOs in addition to the pre-existing right-side cavitary lesion | RTX, AZA, prednisone (7.5 mg) | NR           | No               | None              | HQC, azithromycin | Discharged after 4 d; recovered | On 7.5 mg prednisone at the time of diagnosis |
| Falla11     | 77  | F      | NR        | NR                      | 24                            | PR3       | Scattered bilateral GGOs          | RTX, MTX, prednisone 5 mg | 30            | No               | None              | None              | Discharged after 6 d; recovered | — |
| Sudrez-Diaz12 | 64  | F      | NR        | NR                      | 72                            | MP0       | Prednisone 5 mg                    | Prednisone 5 mg | 90            | No               | None              | None              | Recovered at home | Treated for vasculitis relapse with RTX 90 d before COVID diagnosis |
| Current study  | 74  | F      | African American | 1.5                     | 108                           | MP0       | Prednisone 5 mg                    | Prednisone 5 mg | —            | No               | MV               | Remdesivir        | Recovered          | Renal biopsy showed mild necrotizing GN, received MP 40 mg × 10; RTX 2 mg after COVID diagnosis |
| Current study  | 48  | F      | Hispanic  | 0.7                     | 72                            | PR3       | Diffuse peribronchovascular and peripheral GGOs | RTX 500 mg, prednisone 8 mg | 60           | No               | HFNC              | Remdesivir, Dexamethasone | Recovered          | — |
| Current study  | 81  | F      | African American | 1.5                     | 12                            | PR3       | Scattered bilateral GGOs          | AZA, prednisone 5 mg | —            | No               | HFNC              | None              | Recovered          | — |
| Current study  | 45  | M      | Asian     | 1.3                     | 60                            | PR3       | Scattered bilateral GGOs          | RTX, prednisone 5 mg | 120           | No               | Low-flow, 2 L      | Remdesivir        | Recovered          | — |
| Current study  | 63  | M      | Caucasian | 1.2                     | 0.5                           | PR3       | Scattered bilateral GGOs          | See comments        | 7             | No               | Low-flow, 6 L      | Dexamethasone, remdesivir, convalescent plasma | In-hospital | Received RTX 1 g and MP 500 mg × 3 for induction. Diagnosed with COVID a week after RTX and discharged from hospital. |
| Current study  | 36  | M      | Caucasian | 1                       | 54                            | PR3       | Scattered bilateral GGOs          | RX1               | 80            | No               | None              | None              | Recovered at home | — |

ANCA, antineutrophil cytoplasmic antibody; AZA, azathioprine; COVID, coronavirus disease 2019; CYC, cyclophosphamide; F, female; GGOs, ground-glass opacities; GN, glomerulonephritis; HQC, hydroxychloroquine; HFNC, high-flow nasal cannula; iHD, intermittent hemodialysis; IS, immunosuppression; M, male; MP, methylprednisone; MPD, myeloperoxidase antibody; MTX, methotrexate; MV, mechanical ventilation; NR, not reported; NRB, nonrebreather mask; PR3, proteinase 3; RTX, rituximab; UA, urinalysis.
ACKNOWLEDGMENTS
DG is supported by Gorski Fund.

SUPPLEMENTARY MATERIAL
Supplementary File (PDF)
Supplementary Methods

REFERENCES
1. Kant S, Morris A, Ravi S, et al. The impact of COVID-19 pandemic on patients with ANCA associated vasculitis [e-pub ahead of print]. J Nephrol. https://doi.org/10.1007/s40620-020-00881-3. Accessed December 10, 2020.
2. Guilpain P, Le Bihan C, Foulongne V, et al. Rituximab for granulomatosis with polyangiitis in the pandemic of covid-19: Lessons from a case with severe pneumonia. Ann Rheum Dis. 2020;80:e10.
3. Daniel P, Raad M, Waked R, et al. COVID-19 in a patient treated for granulomatosis with polyangiitis: Persistent viral shedding with no cytokine storm. Eur J Case Rep Intern Med. 2020;7:001922.
4. Pouletty M, Borocco C, Ouldali N, et al. Paediatric multisystem inflammatory syndrome temporarily associated with SARS-CoV-2 mimicking Kawasaki disease (kawa-COVID-19): a multicentre cohort. Ann Rheum Dis. 2020;79:999–1006.
5. Pendergraft WF, Preston GA, Shah RR, et al. Autoimmunity is triggered by cPR-3(105–201), a protein complementary to human autoantigen proteinase-3. Nat Med. 2003;10:72–79.
6. Masuda S, Nonokawa M, Futamata E, et al. Formation and disordered degradation of neutrophil extracellular traps in necrotizing lesions of anti-neutrophil cytoplasmic antibody–associated vasculitis. Am J Pathol. 2019;189:839–846.
7. Zuo Y, Yalavarthi S, Shi H, et al. Neutrophil extracellular traps in COVID-19. JCI Insight. 2020;5:e138999.
8. Schramm MA, Venhoff N, Wagner D, et al. COVID-19 in a severely immunosuppressed patient with life-threatening eosinophilic granulomatosis with polyangiitis. Front Immunol. 2020;11:2086.