Antineutrophil Cytoplasmic Antibody-Associated Vasculitis and COVID-19

The Clinical Course and Prognosis of 15 Patients From a Tertiary Care Center

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Objective: The aim of this study was to evaluate incidence rates, prognoses, and disease-related factors associated with poor outcomes in patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV) who had coronavirus disease (COVID-19).

Methods: Patients with AAV were questioned for a history of COVID-19 in the outpatient setting. Cumulative clinical findings and treatment history were obtained from the patients' medical records. The clinical, laboratory, and imaging findings of inpatients with COVID-19 were recorded. The data of patients who developed symptomatic COVID-19 and/or died of the disease were used for comparison.

Results: Eighty-nine patients (47.2% female; mean age, 56 ± 12.5 years) were included. The diagnosis was granulomatosis with polyangiitis in 56 patients (62.9%) and microscopic polyangiitis in 33 (37.1%). Sixty-one (68.2%) and 21 patients (23.6%) had renal and peripheral nerve involvement, respectively. Ten patients had a history of diffuse alveolar hemorrhage. Fifteen patients (16.9%) had COVID-19, including 9 (60%) with severe pneumonia. Twelve patients (85.7%) were hospitalized, 6 (42.9%) were admitted to the intensive care unit, and 5 (35.7%) died. All deceased patients had hypogammaglobulinemia (IgG levels <700 mg/dL) during hospital admission. Symptomatic COVID-19 was associated with higher organ damage scores, and disease-related factors associated with poor outcomes in patients with AAV were used for comparison.

Conclusions: The prognosis was poor in our patients with AAV who had COVID-19, especially those with severe multisystem involvement. Hypogammaglobulinemia was associated with mortality. Serum IgG level monitoring in patients with AAV would be beneficial during the COVID-19 pandemic.

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patients' medical charts. The Birmingham Vasculitis Activity Score (BVAS) at diagnosis and the BVAS and Vasculitis Damage Index (VDI) score at the beginning of the screening period were calculated from the patients' records retrospectively. Patients were considered as receiving RTX maintenance within 1 year after their last infusion or until they switched to another treatment. Previous IgG measurements were checked, and patients who had hypogammaglobulinemia (hIgG; defined as an IgG level <700 mg/dL) at least once during their follow-up were selected for comparison.

The medical records of patients with a history of hospital admission due to COVID-19 were also evaluated. Probable and confirmed cases of COVID-19 were diagnosed in accordance with the World Health Organization COVID-19 case definition published in December 2020.10 Reverse transcription polymerase chain reaction for SARS-CoV-2, pneumonia severity on thoracic computed tomography (CT), the presence of hypoxemia, intensive care unit (ICU) admission, orotracheal intubation, and death were recorded. The CT findings considered indicative of COVID-19 were ground-glass opacity, consolidation, reticulation, crazy paving pattern, and vascular enlargement, as previously described by Erturk et al.11 The severity of involvement was evaluated on the basis of CT findings by a radiologist and classified as mild, moderate, or severe pneumonia. The statistical data of the patients with severe COVID-19 who were hospitalized and/or who died were compared with those of other patients who developed COVID-19.

COVID-19 treatment was administered to all patients as recommended in the Turkish Ministry of Health guidelines and in accordance with the recommendations after confirming the diagnosis. Hydroxychloroquine (400 mg/d for 5 days, removed from the guideline in August 2020) and favipiravir therapies (1200 mg/d for 5 to 10 days after a 3200-mg loading dose) were administered in accordance with the recommendations during that period. Glucocorticoid therapy (dexamethasone 6 mg/d or methylprednisolone 40–60 mg/d) was given to the patients with hypoxemia and/or findings of hyperinflammatory response (prolonged fever, cytopenia, and increased fibrin degradation products in addition to persistently elevated levels of acute-phase reactants despite treatment). In cases unresponsive to steroids, tocilizumab 400–800 mg or anakinra 300–600 mg/d were given after obtaining patient consent and the approval of the Turkish Republic Ministry of Health. All inpatients with a diagnosis of COVID-19 were screened for hIgG, and a high-dose intravenous immunoglobulin (2 g/kg) was administered if hIgG was present. Ethics committee approval was received from the Istanbul University Istanbul Faculty of Medicine Ethics Committee (date number: 2021-96445). Written informed consent was obtained from patients who visited the hospital, and verbal consent was obtained from patients who were contacted by phone. In this study, SPSS 21.0 version (IBM, Armonk, NY) was used for the statistical analysis of data. Descriptive statistics and discrete and continuous numerical variables were expressed as mean ± standard deviation or median and interquartile range (IQR). Categorical variables were expressed as number of cases with the percentage (n [%]). Statistical analysis was performed to identify factors associated with symptomatic COVID-19, the need for hospitalization, and mortality. Cross-tabular statistics were used to compare categorical variables (χ² and Fisher exact tests). Normally distributed parametric data were compared using Student and paired t tests. Nonparametric data that did not show a normal distribution were compared using the Mann-Whitney U and Kruskal-Wallis tests. The p values of <0.05 were considered statistically significant.

RESULTS

From among the 129 patients with ANCA-associated vasculitis at follow-up, we identified 94 patients with GPA and MPA whose last visit was between December 1, 2019 and February 28, 2021. In 89 patients, data could be gathered and analyzed. None of the 7 patients with EGP A had confirmed COVID-19, and EGPA cases were not included in the study.

This patient group included 42 women (47.2%), with a mean age of 56 ± 12.5 years (range, 28–81 years). The median follow-up time for vasculitis was 60 months (range, 16–272 months). The characteristics and disease activity of AAV in the patients included in this study are summarized in Table 1. Fifty-seven patients had previous IgG measurements during follow-up, of whom 14 (24.5%) had at least 1 measurement indicating the presence of hIgG.

The treatment data are summarized in Table 2. Ten patients (11.2%) attained remission without treatment. One patient was receiving high-dose GC and plasmapheresis in the ICU for a relapse of diffuse alveolar hemorrhage when COVID-19 was detected. We identified 15 patients (16.9%); 14 confirmed cases and 1 probable case of COVID-19 with symptomatic COVID-19 until the end of the screening period. Among these patients, 14 had COVID-19 confirmed using reverse transcription polymerase chain reaction for SARS-CoV-2, and one had severe acute respiratory illness and thoracic CT findings strongly suggestive of COVID-19. Glucocorticoid and RTX treatments, history of hIgG, previous diffuse alveolar hemorrhage, renal involvement, and advanced CKD were associated with the development of symptomatic COVID-19. The mean BVAS and median GC dose at screening were higher in the patients with symptomatic COVID-19 than in those with asymptomatic COVID-19 (Table 3).

The clinical features of the patients with COVID-19 are summarized in Table 4. Severe pneumonia according to CT findings was significantly associated with hypoxemia (8 vs 0: p = 0.001; odds ratio [OR], 9; 95% confidence interval [CI], 1.4–57), ICU admission (6 vs 2: p = 0.003; OR, 4.5; 95% CI, 1.3–15.3), and mortality (5 vs 3: p = 0.01; OR, 3.3; 95% CI, 1.3–8.6). Tocilizumab

| TABLE 1. Characteristics of AAV Patients Included Into the Study |
|-----------------|-----------------|
| Variables       | n (%)           |
| GPA             | 56 (62.9)       |
| MPA             | 33 (37.1)       |
| Anti-PR3 positivity | 46 (51.7)     |
| Anti-MPO positivity | 32 (35.9)     |
| Mean BVAS at diagnosis, mean ± SD | 17.1 ± 7.5 (5–40) |
| Mean BVAS at screening, mean ± SD | 0.5 ± 2.25 (0–15) |
| Remission at the screening (BVAS = 0) | 81 (91)       |
| Upper respiratory tract involvement | 51 (57.3)    |
| Lower respiratory tract involvement | 72 (80.9)    |
| Diffuse alveolar hemorrhage | 10 (10.6)     |
| Renal involvement | 69 (68.2)     |
| Peripheral nerve system involvement | 21 (23.6)    |
| Relapses (ever) | 32 (28)         |
| Serious infections (ever) | 29 (25.8)    |
| Smoker          | 19 (16.9)       |
| CKD (GFR <60 mL/min) | 29 (25.8)     |
| Advanced CKD (GFR <30 mL/min) | 10 (11.2)     |
| On hemodialysis treatment | 3 (3.4)       |
| Hypertension    | 30 (33.7)       |
| Diabetes mellitus | 6 (6.7)        |

MPO, myeloperoxidase; PR3, proteinase.
and anakinra were administered to 1 (6.7%) and 4 patients (26.7%), respectively.

Twelve of the 15 patients were hospitalized for COVID-19. No factors associated with hospitalization were identified. IgG levels were measured in all hospitalized patients, with a mean of 625 ± 267 mg/dL. Eight patients (66%) had hIgG, of whom 3 (25%) had severe hIgG (<400 mg/dL). Hypogammaglobulinemia was detected for the first time in 3 of the 8 patients.

Four of the 5 deceased patients (3 with RTX treatment and 1 with renal transplant) were in remission (BV AS = 0) at the time of COVID-19. The fifth patient who died was treated for a relapse in the ICU. All deceased patients had hIgG during hospital admission due to COVID-19. The mean age, frequency of RTX treatment and trimethoprim-sulfamethoxazole prophylaxis, mean duration between the last RTX dose and the onset of COVID-19, history of relapse or serious infections, and frequency of chronic renal insufficiency were similar between the deceased and surviving patients. Peripheral nerve involvement, higher total VDI score, and the presence of hIgG during hospital admission were found to be associated with mortality (Table 5).

**DISCUSSION**

In this study, we investigated the incidence rate of COVID-19 and factors associated with hospitalization and mortality in patients with AAV after the first year of the COVID-19 pandemic. To evaluate more up-to-date data, patients who visited our hospital within the specified date range were included in this study. Nearly one fourth of our patients with AAV (28/122) did not visit the hospital in 2020, probably because of concerns about infection. The severity of the clinical manifestations in our patients was similar to that reported in recently published studies.

The overall cumulative prevalence of COVID-19 was reported to be 3403.6 per 100,000 population in Turkey at the beginning of March 2021. A considerably high proportion (nearly one fifth) of the patients with AAV who were actively followed up in our clinic during the first months of 2021 had COVID-19.

**TABLE 2.** Treatments of Patients With AAV at the Screening

| Treatment                          | n (%)     |
|-----------------------------------|-----------|
| Glucocorticoids                   | 68 (76.4) |
| Low-dose glucocorticoids (<7.5 mg)| 63 (70.8%)|
| Median glucocorticoid dose (prednisolone/mg) | 5 (0–40) |
| Methotrexate                      | 13 (14.6) |
| Azathioprine                      | 24 (27)   |
| RTX                               | 28 (31.5) |
| Mean duration between last RTX dose to screening, mo | 5 ± 3.5 (1–11) |
| Mycophenolate mofetil             | 5 (5.6)   |
| TMP-SMX prophylaxis               | 47 (52.8%)|

**TABLE 3.** Comparison of Characteristics Between Patients With Symptomatic and Asymptomatic COVID-19

| Characteristics                              | Symptomatic and Asymptomatic COVID-19 (n = 15) | Asymptomatic COVID-19 (n = 74) | p value | OR   |
|----------------------------------------------|-----------------------------------------------|--------------------------------|---------|------|
| Age, mean ± SD                               | 53.4 ± 11.9                                   | 56.6 ± 12.6                    | 0.38    |      |
| Sex (female), %                              | 6 (40)                                        | 35 (47.3)                      | 0.6     |      |
| Disease subgroup (GPA), %                    | 10 (33)                                       | 46 (62.2)                      | 0.74    |      |
| Duration of disease, median (IQR), mo        | 55 (33)                                       | 65 (63)                        | 0.15    |      |
| Lower respiratory tract involvement, %       | 14 (93.3)                                     | 58 (78.4)                      | 0.02    | 4.1  |
| Diffuse alveolar hemorrhage, %                | 4 (26.7)                                      | 6 (8.1)                        | 0.01    | 4.1  |
| Renal involvement, %                         | 14 (93.3)                                     | 47 (63.5)                      | 0.02    | 8    |
| PNS involvement, %                           | 3 (20)                                        | 18 (24.3)                      | 0.7     |      |
| BVAS at diagnosis, mean ± SD                 | 14.8 ± 5.6                                    | 17.6 ± 7.7                     | 0.38    |      |
| BVAS at screening, mean ± SD                 | 1.86 ± 4.3                                    | 0.27 ± 1.4                     | 0.01    |      |
| On GC treatment, %                           | 14 (93.3)                                     | 54 (73)                        | 0.09    |      |
| GC dose (mg prednisolone), median (IQR)       | 5 (0)                                         | 5 (5)                          | 0.025   |      |
| On RTX treatment, %                          | 9 (60)                                        | 19 (25.7)                      | 0.009   | 2.3  |
| Duration between last RTX dose and COVID-19, mean ± SD (n = 28), mo | 5.55 ± 2.9                                   | 4.6 ± 3.8                      | 0.51    |      |
| Serious infection (ever), %                  | 7 (46.7)                                      | 22 (29.7)                      | 0.14    |      |
| Patients who had at least 1 low IgG measurement during their follow-up (n = 57) | 6/14 (42.8) | 7/43 (16.3) | 0.04    | 2.5  |
| Smoker, %                                     | 3 (20)                                        | 16 (21.6)                      | 0.63    |      |
| CKD, %                                       | 7 (46.7)                                      | 22 (29.7)                      | 0.2     |      |
| Advanced CKD (GFR 30 mL/min), %              | 4 (26.7)                                      | 6 (8.1)                        | 0.038   | 3.3  |
| Flares (ever), %                             | 7 (46.7)                                      | 25 (33.8)                      | 0.35    |      |
| Damage (any), %                              | 14 (93.3)                                     | 68 (91.9)                      | 0.85    |      |
| Total VDI score, median (IQR)                | 3 (2)                                         | 2 (2)                          | 0.15    |      |
| Hypertension, %                              | 8 (53.4)                                      | 22 (29.7)                      | 0.08    |      |
| Diabetes, %                                  | 1 (6.7)                                       | 5 (6.8)                        | 0.99    |      |

Statistically significant values (p < 0.05) are marked in bold.

BVAS, Birmingham Vasculitis Activity Score; CKD, chronic kidney disease; GC, glucocorticoid; GPA, granulomatosis with polyangiitis; IQR, interquartile range; PNS, peripheral nerve system; RTX, rituximab; VDI, Vasculitis Damage Index.
TABLE 4. Clinical Features of Patients With COVID-19 and ANCA-Associated Vasculitis

| Chest CT findings                        | n = 15 (%) |
|------------------------------------------|------------|
| Mild pneumonia                           | 2 (13.3)   |
| Moderate pneumonia                       | 3 (20)     |
| Severe pneumonia                         | 8 (53.4)   |
| Hypoxemia                                | 9 (60)     |
| Hospitalization                          | 12 (85.7)  |
| High-dose glucocorticoids (≥50 mg prednisolone/day) | 12 (85.7) |
| Anticytokine (anti-IL-1/IL-6) treatment  | 5 (33.3%)  |
| ICU admission                            | 6 (42.9%)  |
| Death                                    | 5 (33.3%)  |

ICU, Intensive Care Unit.

previous study of patients with AAV from our group, 77 patients were evaluated using a questionnaire, and except for a single patient who died after the diagnosis of COVID-19, no other symptomatic cases were identified. The strict compliance of the patients with quarantine measures during this period was consistent with this result. Loosening protective measures with the prolongation of the pandemic and the relative normalization of social life have been considered the most important reasons for the increased number of cases.

In our study, the incidence of symptomatic COVID-19 was significantly higher in patients with a history of life-threatening organ involvement, advanced CKD, and active disease measured with the BVAS. These patients should be considered significantly vulnerable and to be receiving more intense and higher cumulative doses of immunosuppressive therapy. The association between GC and RTX treatments and the development of symptomatic COVID-19 was similarly consistent with this suggestion.

Among the 15 patients with symptomatic COVID-19, most needed hospitalization, nearly half of the patients (42.9%) needed ICU admission, and one third died. In a study conducted in the United Kingdom and Ireland that included 65 patients with vasculitis (of whom 55 had AAV) who had COVID-19, the hospitalization and mortality rates were similar (8). In this study, GC treatment was also found to be associated with poor prognosis.

We confirmed the results of a previous study that the severity of CT findings was a variable associated with poor outcomes. In addition, peripheral nerve involvement, higher VDI scores, and the presence of hIgG during hospital admission were found to be associated with mortality in patients with AAV. More severe cumulative damage and peripheral nerve involvement were thought to be related to a more severe disease and aggressive treatment leading to mortality.

Growing evidence suggests a poor prognosis in patients with COVID-19 previously treated with RTX therapy. The association between hIgG development after RTX treatment and the development of serious infections in patients with AAV has been reported. In a large study of 1090 patients, among patients with inflammatory rheumatic diseases who were evaluated for COVID-19, those who received RTX therapy developed more severe infections and needed longer hospitalization. In addition, in a follow-up study from the COVID-19 Global Rheumatology Alliance physician-reported registry, patients with rheumatic diseases who were receiving RTX therapy had higher odds of death than those who received methotrexate monotherapy. In our study, 9 of

TABLE 5. Comparison of AAV Patients Who Died Due to COVID-19 and Survivors

|                          | Deceased (n = 5) | Survived (n = 10) | p value | OR   |
|--------------------------|------------------|-------------------|---------|------|
| Age, mean ± SD           | 51.2 ± 12.6      | 54.6 ± 12.1       | 0.6     |      |
| Sex (female), %          | 4 (80)           | 2 (20)            | 0.09    |      |
| BVAS on screening, mean ± SD | 4.2 ± 6.6       | 0.7 ± 2.2         | 0.37    |      |
| Lower respiratory tract involvement, % | 5 (100)       | 9 (90)            | 0.4     |      |
| Diffuse alveolar hemorrhage, % | 1 (20)         | 3 (60)            | 0.6     |      |
| Renal involvement, %     | 5 (100)          | 9 (90)            | 0.4     |      |
| PNS Involvement, %       | 3 (60)           | 0 (0)             | 0.006   | 9 (1.4–57) |
| BVAS on screening, mean ± SD | 4.2 ± 6.6       | 0.7 ± 2.2         | 0.14    |      |
| On GC treatment, %       | 5 (100)          | 9 (90)            | 0.46    |      |
| GC dose (mg prednisolone), median (IQR) | 5 (17.5)   | 5 (0)             | 0.59    |      |
| On RTX treatment, %      | 3 (60)           | 6 (60)            | 1       |      |
| Time between last RTX dose and COVID-19, mean ± SD, mo (n = 9) | 5 ± 1.7 | 5.8 ± 3.5 | 0.65 |
| hIgG during hospitalization (n = 12), % | 5/5 (100) | 1/7 (14.3) | 0.03 | 2.3 (1–5.5) |
| Serious infection ever, % | 3 (60)           | 4 (40)            | 0.57    |      |
| TMP-SMX prophylaxis      | 2 (40)           | 5 (50)            | 0.71    |      |
| Smoker, %                | 1 (20)           | 2 (20)            | 0.77    |      |
| Advanced CKD, %          | 2 (40)           | 2 (20)            | 0.4     |      |
| Flares (ever), %         | 4 (80)           | 3 (30)            | 0.06    |      |
| Damage (any), %          | 5 (100)          | 9 (90)            | 0.46    |      |
| Total VDI score, median (IQR) | 4 (2)           | 2.5 (2)           | 0.04    |      |
| Hypertension, %          | 3 (60)           | 5 (50)            | 0.7     |      |
| Diabetes, %              | 0 (0)            | 1 (10)            | 0.46    |      |

Statistically significant values (p < 0.05) are marked in bold.

BVAS, Birmingham Vasculitis Activity Score; CKD, chronic kidney disease; GC, glucocorticoid; IQR, interquartile range; PNS, peripheral nerve system; RTX, rituximab; TMP-SMX, trimethoprim-sulfamethoxazole; VDI, Vasculitis Damage Index.
the 15 patients who had COVID-19 were receiving RTX treatment, which was not found to be associated with mortality. On the other hand, the association between RTX therapy and poor outcomes, as shown in previous studies, might be attributable to treatment-related hIgG. Hypogammaglobulinemia was also reported to be associated with severe COVID-19 in patients with hematological malignancies (especially those treated with anti-CD20 therapies) and immunodeficiencies. Impaired humoral immune response and late neutralizing IgG development have been shown to be associated with mortality in patients with COVID-19. We suggest that humoral immunodeficiency caused by RTX treatment leads to a poor prognosis with a similar mechanism.

This study has several limitations due to its retrospective nature and limited number of patients. As polymerase chain reaction or antibody screening for the entire cohort was not performed within the scope of the study, we could not identify asymptomatic patients and could not determine the true incidence of COVID-19. However, we collected most patient data from our AAV cohort and gathered significant information on the disease course of symptomatic COVID-19. Studies have evaluated severe diseases and poor prognostic factors, as explained above. However, our study has the advantage of investigating the factors affecting the course and prognosis of symptomatic COVID-19. We did not perform a multivariable analysis because of the small number of cases; therefore, our results should be interpreted with caution and confirmed in a future study.

Another limitation of our study is the lack of previous IgG measurements in some patients. IgG levels were measured only in patients who received RTX treatment and had a history of serious infections. To overcome this limitation, we analyzed and presented the data of 57 patients (64%) who had previous measurements. Moreover, IgA and IgM levels were not routinely measured in patients with AAV and were not presented in our study.

In conclusion, the prognosis of COVID-19 was found to be poor in patients with AAV who had severe multisystem involvement, higher disease activity, and permanent organ damage, confirming the findings of previously published studies. We suggest that the development of hIgG during RTX and/or other immunosuppressive treatments may be a factor associated with mortality in patients with AAV, and serum IgG level monitoring and IgG replacement therapy should be considered for these patients.

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