A single center survey study of systemic vasculitis and COVID-19 during the first months of pandemic

Abstract

Introduction: COVID-19 pandemic created concerns among patients receiving immunosuppressive therapy. Frequency of COVID-19 and impact of lockdown on treatment compliance in patients with vasculitis are largely unknown.

Patients and method: Patients with ANCA-associated and large vessel vasculitis that have been followed-up in our clinic were contacted by phone and a questionnaire containing home isolation status, treatment adherence and history of COVID-19 between March 1st and June 30th, 2020 was applied.

Results: The survey was applied to 103 patients (F/M: 59/44, mean age: 53.2±12.5). Thirty-three (32%) patients didn't attend at least one appointment; 98(95.1%) noted that they spent 3 months in home isolation. Five patients (4.8%) received immunosuppressives irregularly and 3(2.9%) developed symptoms due to undertreatment. Four (3.9%) patients admitted to hospital with a suspicion of COVID-19, but none of them had positive PCR or suggestive findings by imaging. COVID-19 diagnosed in a patient with granulomatosis with polyangiitis during hospitalization for disease flare and she died despite treatment.

Discussion: Frequency of COVID-19 was low in patients with vasculitis in our single center cohort. Although outpatient appointments were postponed in one-third of our patients, high compliance with treatment and isolation rules ensured patients with vasculitis overcome this period with minimal morbidity and mortality.

Key Words: COVID-19, ANCA-associated vasculitis, large vessel vasculitis, treatment adherence, compliance

Introduction

The COVID-19 pandemic has created an alarming situation in patients with autoimmune disease receiving immunosuppressive treatment, in terms of predisposition to infection. There is limited data on the effect of rheumatic disease and immunosuppressive therapy on the prognosis of COVID-19 disease. Monti *et al* suggested that the presence of rheumatic disease will not negatively affect the course of COVID-19; whereas Gianfresco *et al* reported that the use of corticosteroids (CS) above 10 mg/day increases hospitalization. It was reported that the use of anti-TNF agents reduces the risk of hospitalization [1, 2]. Among the autoimmune diseases, systemic vasculitis constitutes a variety of conditions including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), Takayasu arteritis (TA), and giant cell arteritis (GCA). These rare diseases can cause morbidity and mortality, however the additional effect of COVID-19 on prognosis of systemic vasculitis is yet unknown.

In Turkey, over two hundred thousand COVID -19 cases were reported between March-June 2020. Most of the cases were residing in Istanbul. In order to prevent the spread of COVID-19, the following measures were taken: periodic curfews and quarantine were implemented; employees receiving immunosuppressive therapy were given administrative leave and patients allowed to receive their routine treatment without prescription. Some health institutions have been transformed into "pandemic hospitals" and most inpatient units had served COVID-19 patients, during this period. Physicians of all branches, including internal medicine and rheumatology specialists, were assigned to these COVID-19 units periodically. Therefore, outpatient appointments significantly decreased and periodic follow-up visits were postponed.

This situation caused disruption or delay in the treatment of patients, especially for those with vital organ involvement.

In a survey study including 770 patients followed-up in rheumatology clinics, 22% of them were reported to be non-compliant with treatment due to concerns about infection [3]. Considering the complications due to possible disease flares, treatment compliance is an important issue [4]. In our study, we aimed to evaluate the effect of COVID-19 and the quarantine period on disease activity and treatment compliance in patients with various systemic vasculitis, by applying a telephone survey to our patients who have been regularly followed up in our vasculitis clinic.

Patients and methods

Patients with GPA, MPA, TA, and GCA who have been followed by the Department of Rheumatology at Istanbul Faculty of Medicine, and whose last outpatient visit were after July 1st, 2019, were included in this study. Ethics committee approval was received from the Istanbul University Istanbul Faculty of Medicine Ethics Committee (Date-Number: 2020-937).

Each patient was reached out by phone calls from 20/07/2020 to 31/07/2020. Patients who had at least one outpatient visit in between 1 March - 30 June 2020 were excluded and assessed separately. After reading the voluntary consent form verbally and obtaining consent from the patients, an 11-question-survey was applied to the participants (Table 1). Patients with hospital admission and/or hospitalization history were invited to the clinic and their records were evaluated. The survey data were evaluated by being digitized using the IBM SPSS Statistics for Windows (Version 21.0. Armonk, NY: IBM Corp) program. The

continuous variables are presented as the mean (SD) or median (IQR), whereas the categorical variables are presented as a number and percentage. Normality tests were performed with Kolmogorov-Smirnov or Shapiro tests. For categorical comparisons, the Chi-square and Fisher's tests were used. Student's t-test and Mann-Whitney U test were used for the comparison of continuous variables, according to the normality of the data. A p value less than 0.05 was accepted as statistically significant.

Results

In a cohort of 211 patients with vasculitis whose last visit were within one year, forty-nine patients with systemic vasculitis (30 AAV, 15 TA, 4 GCA) attended their outpatient appointment between March 1 and June 30. None of these patients reported symptoms that might be associated with COVID-19 (fever, upper or lower respiratory system symptoms, nausea or diarrhoea). After exclusion of these patients, a total of 103 available patients (F / M: 59/44, median age: 57±15.4 (25-84)) were included into the survey by phone call (Figure). Patients were being followed up with the diagnosis of GPA;54 (52.4%), MPA; 15 (14.5%), TA;22 (21.4%), GCA;12 (11.6%).

The mean follow-up period was 84.6 ± 51.4 months (9-251). Fifty-four (52.4%) patients were receiving only oral drugs, 41 (39.8%) parenteral treatment and 8 (7.8%) patients were followed up without treatment. Patient characteristics were described in table-2. Eighty-five patients (82.5%) were on corticosteroids. Thirty-five (33.9%) patients were receiving intravenous treatments requiring periodic hospital admissions (26 Rituximab (RTX), 6 Infliximab (IFX), 1 Cyclophosphamide (CYC) (monthly pulse), 2 intravenous Immunoglobulin (IVIG)).

The average time from the last appointment to the survey date was 5.2 ± 2.6 (1-12) months. Thirty-three (32%) patients missed at least one outpatient appointment. Patients with a diagnosis of AAV and LVV were 24 and 9, respectively. Six of these patients (18.2%) were on parenteral treatment (3 RTX, 2 Tocilizumab, 1 CYC (monthly pulse)). There was no statistically significant difference between these groups in terms of age, sex and disease subtypes (table-3). Attendance rate for appointments was higher among patients who use parenteral treatment in comparison to oral treatment (35/41 vs. 31/54 p=0.003 OR:2.9 %95 CI 1,3-6,5).

Ninety-eight patients (95.1%) spent 3 months in home isolation while 2 (1.9%) patients continued to work. Thirty-eight (36.9%) patients' relatives who live in the same house continued working. Among the relatives of these patients, three (2.9%) were treated as outpatients with the diagnosis of COVID-19 but all were RT-PCR negative. Five (4.8%) patients (1 GPA, 2 TA, 2 GCA) stated that they received their treatments irregularly during this period. One TA patient was receiving azathioprine; four patients were receiving parenteral therapy (table-4). All patients stated that they did not use their treatment regularly due to concerns about immunosuppressive therapy during pandemic. Symptoms were thought to be developed due to undertreatment in three of the patients (2.9%), and treatment was restarted in these patients after COVID-19 had been ruled out.

Four patients (3.9%) (2 GPA, 1 TA and 1 GCA) stated that they applied to the hospital with a suspicion of COVID-19 in the 3-month period. COVID-19 RT-PCR tests and thorax CT imaging were negative in all four patients and they received symptomatic treatment only.

Our survey revealed that two patients who were called had died earlier. Patient #1 was a 60-year-old patient with a 5-year history of GPA and 1-year history of metastatic bladder carcinoma. His last outpatient appointment was in December 2019. The assessment of records showed that he was in remission under low-dose CS treatment and died due to pericardial metastasis of carcinoma and cardiac tamponade before the pandemic period (January 2020).

Patient #2 was a 37-year-old female patient with GPA diagnosed in 2006. She developed end-stage renal failure during disease course. She was in clinical remission in her last outpatient visit in December 2019, despite her high titer anti-PR3 positivity. She missed her follow-up visit in April 2020 due to the quarantine process, later on she was admitted in Intensive Care Unit (ICU) in May 2020 due to diffuse alveolar haemorrhage. Before the admission, the patient stated that she was compliant with her treatment and she had no known COVID-19 contacts. During induction therapy with high dose corticosteroids and plasmapheresis, her control COVID-19 RT-PCR resulted positive. Tocilizumab (400 mg IV) was administered due to development of macrophage activation syndrome on the 7^{th} day but after 16 days of ICU follow-up, she died due to sepsis and multiorgan failure.

Discussion

In this study, we aimed to determine the effects of the pandemic on the clinical course in patients with systemic vasculitis and the frequency of COVID-19 in our patient population. Nearly half of our patients, most of whom are diagnosed with small vessel vasculitis, have been receiving parenteral treatment and one-third have been receiving intravenous treatments that required periodic hospitalization. Five patients were non-compliant with their treatment and 4 (80%) of these patients were followed up with the diagnosis of large vessel vasculitis. Considering that the majority (67%) of the patients surveyed had ANCA-associated vasculitis

(AAV), although nearly forty percent (24/64) of these patients skipped at least one visit, it was concluded that the treatment compliance of these patients were acceptable. Low rate of treatment inadherence during this period may be related to awareness of the patients about the clinical course of their disease and their use of oral treatment options. Hospital admission requirement for intravenous treatments was thought to be the main reason for the higher rate of attendance to clinic appointments in patients using parenteral drugs.

Our inpatient and outpatient clinics remained open during the 3-month period and all patients received their infusion treatments except for one GPA patient (2.9%) who received monthly intravenous cyclophosphamide treatment. In a survey study conducted in the Lombardy region of Italy, revealed that higher proportion of patients (15%) TA patients who received infliximab treatment could not continue their infusion treatments [5]. Especially in this patient group with severe organ and/or life-threatening disease involvement, higher sustainability of treatment was considered to be one of the most important factors in low mortality. Furthermore, rarity of evident disease exacerbation during the study period supports this view.

During the 3-month period, four (3.9%) patients were admitted to emergency outpatient clinics with various complaints, all of them were found to have negative COVID RT- PCR tests without clear evidence of COVID-19 by thorax imaging. COVID-19 was excluded in these patients due to their asymptomatic course and negative RT-PCR tests. Our patients have low COVID-19 prevalence, which may be related to the patient's awareness of their high-risk status about COVID-19 due to receiving immunosuppressive treatment and as a result compliance with preventive measures. Also, their family members or close contacts may contribute to this outcome with prioritizing preventive measures. Since the results of the

COVID-19 seroprevalence study conducted in our country have not been published yet, it was not possible to compare the prevalence of infection in the study group with the normal population.

The patient with GPA who was hospitalized in the intensive care unit (ICU) with alveolar hemorrhage, was administered tocilizumab due to the findings of COVID-19 associated macrophage activation syndrome. During follow-up, she died due to possible secondary bacterial infection. Based on the data regarding endothelial dysfunction and microvascular thrombosis in COVID-19 patients [6]; it can be speculated that; infection may have triggered disease relapse in our patient. Thus, it is plausible that coexistence of these two conditions had worsened the prognosis.

Our study is one of the first studies with a considerable number of patients with systemic vasculitis in Turkey during the COVID 19-pandemic. Patients are followed-up in a single center and the survey is conducted by the clinicians who follow the patients; these may be important in terms of representing the clinical data more accurately and detecting treatment interruptions more reliably.

In order to prevent hospital acquired infections during the pandemic, the telephone-survey is a useful method with known limitations such as high number of unavailable or refusing patients and lack of detailed answers. Due to the high risk of infection, patients without complaints were not invited to the hospital, which prevented the evaluation of disease activity or other unexpected effects in these patients. Considering that the study covers the first 4 months of the pandemic, the psychological and physical effects of the prolonged period on patients are unknown. Also, the rate of COVID-19 in our cohort was thought to be low due to tight restrictions in first months of pandemic, making it difficult to evaluate the clinical course of

COVID-19 in patients with vasculitis in detail. Antibody screening could not be performed during this period due to insufficient sensitivity and standardization of the readily available COVID-19 antibody kits.

As a result, clinical COVID-19 was rare in systemic vasculitis patients with follow-up in our center during the initial months of the pandemic. Although outpatient appointments were postponed in approximately one-third of the patients, a high rate of compliance with treatment and infection prevention precautions suggested that vasculitis patients managed to overcome this process with minimal morbidity and mortality so far. Multi-center cohorts with longer follow-up are needed to improve our understanding of the course of COVID-19 in patients with systemic vasculitis.

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Table 1. Questions of survey applied to the participants

Questions
1- When was your last outpatient appointment?
2- Which medications do you take regularly?
3- Did you take your medications regularly during past 3 months?
4- Was there any interruption or delay in your treatments you received regularly in hospital settings?
5- Have you had any complaints that you think are related to your illness?
6- Did you continue to work during the pandemic?
7- Did you self-isolated at home during pandemic?
8-Have you applied to a health institution with complaints such as fever, cough, shortness of breath, smell and taste, abdominal pain and diarrhea in the 3-month period?
If yes: - Was a nose or mouth sample collected for COVID-19 there? - If so, do you know the result? - Did you need to be hospitalized with the diagnosis of COVID-19?
9-Did your households members continued to work?
10-Have any of your household members applied to a health institution with complaints such as fever, cough, shortness of breath, smell and taste, abdominal pain and diarrhea in the 3-month period?
If yes: - Was a nose or mouth sample collected for COVID-19 collected? -If so, do you know the result?
11- If you continue to work, has anyone in your work environment been diagnosed with COVID-19?

COVID-19: Coronavirus disease-19

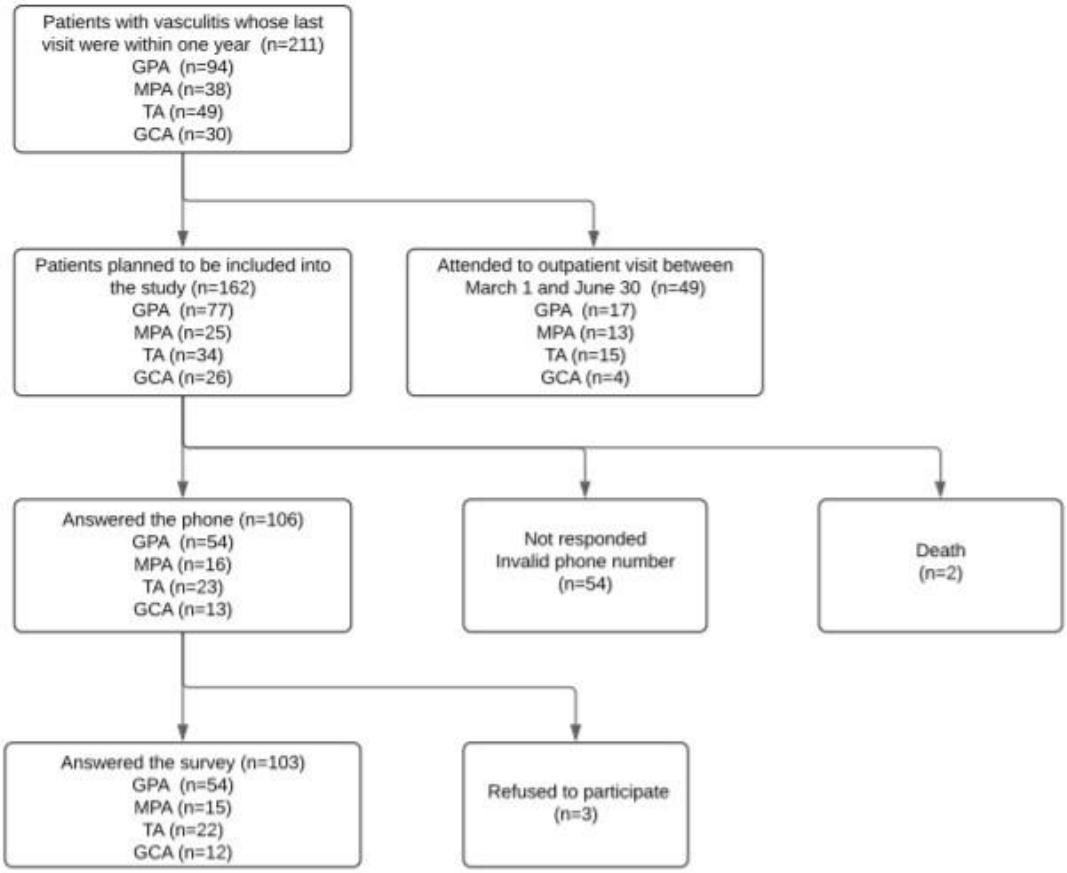

Figure. Flowchart of participation into the study. GCA: Giant cell arteritis, GPA: Granulomatosis with polyangiitis, MPA: Microscopic polyangiitis, TA: Takayasu arteritis

Table-2. Patient characteristics.

	ANCA Associated Vasculitis		Large Vessel Vasculitis	
	GPA (n=54)	MPA (n=15)	TA (n=22)	GCA(n=12)
Age (median±SD; (IQR))	51±16 (24)	57±15.2 (15)	39±13.5 (21.5)	71±9.4 (8.5)
Sex (F/M)	26/28	6/9	20/2	8/4
PR3-ANCA (+)	33	0	-	-
MPO-ANCA (+)	10	14	-	-
LRS involvement	45	11	-	-
Renal involvement	36	10	-	-
Peripheral nerve involvement	5	4	-	-
Chronic renal disease	18	6	2	0
Patients skipped at least one outpatient visit	20	4	5	4
Patients with treatment inadherence	1	0	2	2

AAV: ANCA associated vasculitis, GCA: Giant cell arteritis, GPA: Granulomatosis with polyangiitis, LRS: Lower respiratory system, LVV: Large vessel vasculitis, MPA: Microscopic polyangiitis, MPO: Myeloperoxidase, PR3: Proteinase-3 TA: Takayasu arteritis

Table-3. Comparison of patients who skipped and did not skip their appointments.

	Patients who skipped at least one appointment (n=33)	**Patients who did not skip appointment (n=70)**	**p**
Male sex (%)	15 (62.5%)	24 (34.3%)	0.27*
Age (median±SD; IQR)	59±16.1; 24	51.5±15.1; 22.3	0.3^{Ŧ}
AAV / LVV	24/9	44/26	0.32*

AAV: ANCA associated vasculitis, IQR: Interquatile range, LVV: Large vessel vasculitis, SD: Standard deviation, *chi-square test ^{Ŧ}Mann-Whitney U test

Table-4. Description of patients who had treatment inadherence during 3-month period.

	Age	Diagnosis	Treatment	Skipped doses	Complaint	Final assessment
Case #1	63	GPA	CS + CYC (monthly)	2	none	Treatment restarted
Case #2	48	TA	Tocilizumab (weekly)	4	back pain, arm cladicaution	Patients' complaints diminished after re-admission of treatment
Case #3	38	TA	CS + AZA	Used half dose at her own will	back pain	After negative COVID-19 RT PCR result, complaints are thought to be due to disease activity and treatment restarted
Case #4	73	GCA	Tocilizumab (weekly)	unknown	none	Treatment restarted
Case #5	67	GCA	Tocilizumab (weekly)	12	weakness, fever	After negative COVID-19 RT PCR result, complaints are thought to be due to disease activity and treatment restarted

AZA: Azathioprine, CS: Corticosteroids, CYC: Cyclophospamide, GCA: Giant cell arteritis, GPA: Granulomatosis with polyangiitis, TA: Takayasu arteritis