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Research Article

The Outcomes of COVID-19 Infection in Rheumatic Diseases in Stable Disease Condition: A Case Series Study

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Abstract

Background: The COVID-19 pandemic raised many concerns regarding patients with autoimmune rheumatic diseases (ARD) namely considering the potentially harmful effects of this infectious disease as well as the consequences of the immunosuppressant therapy applied.

Aim: To evaluate the presentations and outcome of COVID-19 in various ARD in stable conditions.

Methods: This is a consecutive clinical series study of 18 outpatient ARD patients (eight systemic lupus erythematosus (SLE), two SLE associated with antiphospholipid syndrome (APS), one patient with primary APS, five with rheumatoid arthritis, one with polymyalgia rheumatica, and one with Still syndrome), who was diagnosed with COVID-19. Data were collected between May 2020 and February 2021, during scheduled visits at a non-covid center, where patients were monitored regularly. We analyzed the presence of the following clinical symptoms: persistent fever higher than 37·5°C, non-productive cough, fatigue, myalgias, arthralgias, anosmia, ageusia, headache, nausea, vomiting, diarrhea, and dyspnea. The onset date and duration of these symptoms, prescribed medications, and management of background medications were also evaluated.

Results: In this case series of ARD patients in a stable disease condition, nine patients were treated with prednisolone, nine patients with hydroxychloroquine, six patients were on Aspirin, and five on methotrexate. None of the patients had interstitial pneumonia, clinical manifestations of COVID-19 were mild, and none were hospitalized. Less than half of the patients (8 of them) had a fever. All patients in a post-covid period were feeling well, without thrombotic complications.

Conclusion: All ARD patients analyzed, presented in a stable disease condition, had been diagnosed with a mild form of COVID-19, not requiring hospitalization. The stable disease condition might be the most important prognostic factor regarding the severity of COVID-19 and its prognosis in this population of patients.

Keywords: COVID-19; Autoimmune Rheumatic Diseases

Introduction

COVID-19 caused by the novel severe acute respiratory syndrome (SARS) coronavirus-2 (CoV-2) is a highly contagious infection presented in various forms: most patients experience mild or subclinical forms of the disease that do not require hospital admission, and a relatively high percentage of patients (40% to 45%) remain asymptomatic [1-3].

It is well known that patients with underlying comorbidities, namely diabetes, obesity as well as cardiovascular and lung diseases, represent a high-risk population [4,5]. People with autoimmune rheumatic diseases (ARD), already recognized as vulnerable to infectious diseases, especially those on immune-suppressants or immune-modulating drugs, might be a population at a higher risk for the development of severe forms of COVID-19 [6]. Furthermore, infectious diseases have long been considered as one of the triggers for ARD [7].

Various studies on SARS-CoV-2 infection in ARD patients reported heterogeneous data regarding the rate and outcome of COVID-19 in this heterogeneous group of patients [8,9]. Furthermore, several emerging reports show that COVID-19 could lead to autoimmune and autoinflammatory disease [10-14]. Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects predominantly women and considers a composite of interactions between genetics, hormones, and environmental factors. In addition, patients are frequently treated with immunosuppressive agents and cytotoxic drugs to control abnormal immune responses and tend to be immunocompromised and more susceptible to infections [15-17]. For that reason, it is reasonable to consider people with SLE as a vulnerable population regarding COVID-19 [18]. In this concise report, we are introducing COVID-19 clinical presentation in SLE and other ARD, focusing on features of stable disease conditions, and their management.

Patients and Methods

This is a consecutive clinical series study of 18 outpatient ARD patients (9 SLE, 1 SLE associated with antiphospholipid syndrome (APS), one patient with primary APS, 5 with rheumatoid arthritis, one with polymyalgia rheumatica, and one with Still syndrome), who was diagnosed with COVID-19.

Among 10 SLE patients, there were 9 females and 1 male, mean age 44.0 ± 13.0 years (≥4 ACR criteria (4-11, mean 7)) with low disease activity: mean SLEDAI for SLE patients was 3.2. One patient had APS associated with SLE, (female, age 51). The median age for all SLE patients was 48.5 ± 9.06 years, and disease duration was 10.6 +/- 7.7 years. Patients (n = 5) with RA (2 females and 3males; mean age 45.00 ± 11.96 years) had also low disease activity (DAS28-ESR < 3.2).

As a part of a regular therapeutic regime, half of our patients have received lower doses of Prednisolone (10 mg daily) and Hydroxychloroquine (HCQ) 400 mg daily) for at least two years before COVID-19 occurrence; 6 patients received lower doses of Aspirin (100 mg daily) and 5 RA patients have been treated with Methotrexate, 10 mg weekly.

In our cohort of ARD patients 33.3% SLE, 40.0% of RA along with one patient with Polymyalgia rheumatica had hypertension which was adequately controlled, and two RA patients were current smokers. The clinical characteristics of our cohort of ARD patients are depicted in table 1.

ARD (N)	Gender (F/M)	Age (years)	Disease activity (mean SLEDAI/ DAS28-ESR)	Therapy	Comorbidities (N/%)
SLE (9)	8/1	44.0 ± 13.0	3.2	OP 10 mg + HCQ 200 mg	Hyp-T (3/33.3)
SLE/APS (1)	1/0	51y		OP 10 mg + HCQ 400 mg + A 100 mg	None
Primary APS (1)	1/0	41	/	A 100 mg + HCQ 400 mg	None

RA (5)	2/3	45.0 ± 12.0	< 3.2	MTX 10 mg	Hyp-T (2/40.0) Current smokers (2/40.0)
Mb Still tardus (1)	1/0	37y	/	OP 10 mg + HCQ 200 mg	None
Polymyalgia rheumatica (1)	1/0	73y	/	OP 10 mg + HCQ 400 mg + A 100 mg	Hyp-T

Table 1: Summarize the ARD patients' clinical characteristics.

*ARD - Autoimmune Rheumatic Disease, SLE - Systemic Lupus Erythematosus, APS - Antiphospholipid Syndrome, RA - Rheumatoid Arthritis, F - Female, M - Male, HCQ - hydroxychloroquine, OP - Oral Prednisolone, A - Aspirin, MTX - Methotrexate, Hyp-T - Hypertension,

Data were collected between May 2020 and February 2021, during scheduled visits at a non-covid center, where patients were monitored regularly. In all patients, the survey (in the form of a pre-established interview) aimed to investigate the occurrence of symptoms possibly related to SARS-CoV-2 infection since the beginning of the COVID-19 pandemic has been established. As a part of the survey, the presence of the following clinical symptoms was investigated: persistent fever higher than 37·5°C, non-productive cough, rhinorrhea, fatigue, myalgias, arthralgias, anosmia, ageusia, headache, nausea, vomiting, diarrhea, and dyspnea. The onset date and duration of these symptoms, prescribed medications, and management of background medications were also evaluated.

All patients have met the American College of Rheumatology (ACR) classification criteria for SLE [19] and revised Sydney criteria for APS [20]. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [21-24] and DAS28-ESR scores for RA activity have been used for the presentation of disease activity at the time of COVID-19 infection [25,26].

For the diagnosis of COVID-19, WHO interim guidance has been used [27,28] and SARS-CoV-2 infection confirmed by real-time reverse transcription-polymerase chain reaction assay (Shanghai bio-germ Medical Technology Co) [28]. We did not have (even national) possibility to test which variant of COVID-19 was present. Radiologic assessments included chest CT and all laboratory testing (a complete blood cell count, blood chemical analysis, coagulation testing, assessment of liver and renal function testing, C-reactive protein, creatine kinase, and lactate dehydrogenase) were performed at the diagnosis and repeated according to the clinical care needs of the patient. As part of the survey, the presence of the following clinical symptoms was investigated: persistent fever higher than 37·5°C, non-productive cough, rhinorrhea, fatigue, myalgias, arthralgias, ageusia/hyposmia, headache, nausea, vomiting, diarrhea, and dyspnea (Table 2). The onset date and duration of these symptoms, prescribed medications, and management of background medications were also evaluated. ARD therapeutical protocols remained the same during COVID-19 infections.

Symptom	SLE (N = 9)	SLE/APS (N = 1)	Primary APS (N = 1)	RA (N = 5)	Mb Still tardus (N = 1)	Polymyalgia rheumatica (N = 1)	ARD (N = 18)
	N pts with symptom			N pts with symptom			
Fever	3 (33.3%)	-	1 (100%)	2 (40%)	1 (100%)	1 (100%)	8 (44.4%)
Fatigue	6 (66.7%)	-	1 (100%)	2 (40%)	-	-	9 (50.0%)
Myalgia/arthralgia	6 (66.7%)	-	-	4 (80%)	-	-	10 (55.5%)
Ageusia/anosmia	7 (77.8%)	1 (100%)	1 (100%)	4 (80%)	-	1 (100%)	14 (77.8%)
Headache	1 (11.1%)	1 (100%)	-	-	-	-	2 (11.1%)

Dyspnea	1 (11.1%)	-	-	-	-	-	1 (5.55%)
Cough	3 (33.3%)	1 (100%)	-	-	1 (100%)	1 (100%)	6 (33.3%)
Nausea/vomiting	3 (33.3%)	-	-	1 (20%)	-	-	4 (22.2%)
Diarrhea	1 (11.1%)	-	-	1 (20%)	-	-	2 (11.1%)

Table 2: Distribution of clinical findings in ARD patients with COVID-19.

*ARD - Autoimmune Rheumatic Disease, SLE - Systemic Lupus Erythematosus, APS - Antiphospholipid Syndrome, RA - Rheumatoid Arthritis

Before the survey was taken, all patients gave their informed consent. It was performed following the ethical standards of the institutional research committee and with the Helsinki Declaration (Ethical Principles for Medical Research Involving Human Subjects) and its later amendments.

Results

The most common symptom in SLE patients was anosmia (77.8%) as in RA patients (80%). Myalgia/arthralgia and fatigue were also often present in SLE patients (66% both) as in RA (80%). Arthralgia as only symptom of COVID-19 was present in two RA patients, but they reported different sensation than as a symptom of disease activity.

As presented in table 2, the most common COVID-19 symptom was anosmia/ageusia and it occurred in 77.8% of all patients. 50% of ARD patients reported fatigue, 55.5% had myalgia and arthralgia during the acute phase of the disease and for several weeks thereafter. Interestingly, none of the patients had interstitial pneumonia (all COVID-19 patients had chest X-ray radiography at the time of diagnosis), clinical manifestations of covid-19 were mild and none of the patients was hospitalized. Furthermore, less than 50% of patients (8 of them) had a fever. There was no worsening of the symptoms of the underlying disease after SARS-CoV-2 infection.

All patients were advised to be vaccinated against COVID-19 infection, a few months after negative RT-PCR test.

Discussion

The pandemic of SARS-CoV-2 infection from its outbreak at the end of 2019 confronted a human population to the largest public health emergency in the last century. Although initially appreciated as respiratory disease, now is considered as a system, multiorgan disease with coagulopathy and hyper inflammation in its ground [29,30].

HCQ is a cornerstone in the treatment of patients with SLE [31]. It is efficient in controlling disease activity and preventing flare as well as in preventing damage accrual and in the improvement of survival [32,33]. Furthermore, HCQ, considered to have an impact on viral load, was a part of initial COVID-19 therapeutical protocols [34,35]. Bhimraj., *et al*. in their analysis of three randomized controlled trials (RCT) and six comparative cohort studies on the possible efficacy of HCQ in COVID-19 failed to show any benefit in terms of viral clearance or prevention of disease progression [36]. In a study by Mathian., *et al*. it was concluded that HCQ does not seem to prevent COVID-19, at least its severe forms, in patients with SLE, although having blood concentrations of the drug within therapeutic range [37]. Recently published RCT conducted on 500 hospitalized mild COVID-19 patients also failed to prove the efficacy of HCQ towards disease progression as well as in sustained viral clearance [38]. However, due to its antithrombotic properties documented in APS therapy, HCQ might be considered a good candidate for the prevention of thrombotic events in COVID-19 patients in association with anticoagulants and its repurposing deserves further evaluation [39,40].

Considering the presentation of COVID-19 in the largest worldwide case series of 3729 ARD patients diagnosed with COVID-19 included in the Global Rheumatology Alliance registry, less than half of (49%) were hospitalized, and 10.5% died [41]. COVID-19-related death was associated with older age, male sex, specific comorbidities, and disease-specific factors (disease activity and specific medications) in this population of patients. The authors concluded that adequate disease control, preferably without increasing glucocorticoid dosages is of utmost importance in this population of patients considering COVID-19 risks.

Euro-COVIMID, a large, multicenter cross-sectional study of patients with ARD (rheumatoid arthritis, axial spondylarthritis, systemic lupus erythematosus, Sjögren's syndrome, or giant cell arteritis) analyzed the serological and clinical prevalence of COVID in six tertiary referral centers in France, Germany, Italy, Portugal, Spain, and the UK [42]. In this study, the occurrence of symptomatic COVID-19 was associated with higher C-reactive protein concentrations (p = 0·038), a median daily dose of prednisone (p = 0·0058), and several disease flares (p = 0·0018), but lower use of biological therapy (p = 0·0009) and lower prevalence of current smoking (p = 0·0085).

In our case series report, we confirmed the importance of adequate treatment and control of ARD in the COVID-19 pandemic to enable the stable condition of the disease which seems to be the most important prognostic factor regarding the severity of the COVID-19 disease and its prognosis.

None of our patients at the time of the enrollment received COVID 19 vaccine but, taking into account its possible course in SLE patients, we strongly recommend that patients with autoimmune rheumatic diseases should receive the COVID-19 vaccines and should be prioritized before the general population [43,44].

Limitation of the Study

The sample size of this study is rather small, and the conclusion still needs to be further confirmed by a larger sample size and prospective cohort studies.

Conclusion

All of the ARD patients, in this case, series, who have already been treated several years before with low doses of prednisolone in combination with HCQ, experienced a mild form of COVID-19 infection with no interstitial pneumonia and no need for in-hospital treatment of the disease. We can only speculate that this treatment had a preventive impact, contributing to the hyperinflammatory and vascular pathogenesis of COVID-19. The stable disease condition of SLE as other ARD might be the most important prognostic factor regarding the severity of COVID-19 and its prognosis in this population of patients.

Conflicts of Interest

Authors declare no conflicts of interest.

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