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Disease Course in Hospitalized COVID-19 Patients with and without Rheumatic Disease and Its Relationship with Immunosuppressive Drug Use

Hastanede Yatan COVID-19 Hastalarında Romatolojik Hastalığı Olan ve Olmayanlarda Hastalığın Seyri ve İmmünsüpresif İlaç Kullanımı ile İlişkisi

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¹University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital, Clinic of Rheumatology, Bursa, Turkey

²University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital, Clinic of Geriatrics, Bursa, Turkey

³Uşak University Faculty of Medicine, Department of Hematology, Uşak, Turkey

Abstract

Introduction: This study aims to determine the course of Coronavirus disease-2019 (COVID-19) with rheumatic diseases (RDs) and to evaluate the effects of immunosuppressive (IS) drugs on the severity of COVID-19.

Materials and Methods: A total of 1905 patients comprising 988 women and 917 men were hospitalized for COVID-19 and were retrospectively analyzed. A total of 57 of them were rheumatic patients (RPs). Rheumatic patients and non-RPs were compared in terms of IS drugs, demographic characteristics, comorbidities, drugs used in the treatment of COVID-19, laboratory and thorax tomography results, and duration of hospitalization (DOH), intensive care unit (ICU), and mortality rates. Patients taking IS drugs were determined as IS patients. Immunosuppressive and non-IS patients were also compared. The effects of each IS drug on the presence of pneumonia, DOH, ICU, and mortality frequency, and poor prognostic factors were further evaluated.

Results: Pneumonia ($p=0.358$), DOH ($p=0.650$), ICU ($p=0.386$), and mortality rates ($p=0.386$) were non significant between RPs and non-RPs. Duration of hospitalization ($p=0.881$), ICU ($p=0.176$), and mortality rates ($p=0.176$) between patients with RDs receiving IS and not receiving IS drugs were also non significant. Intensive care unit ($p=0.003$) and mortality ($p=0.035$) rates were significantly higher in RPs receiving sulfasalazine (SSZ). Rheumatic patients receiving cyclosporine A (CsA) had significantly less pneumonia ($p=0.040$). C-reactive protein level was significantly lower in RPs receiving CsA ($p=0.022$) and hydroxychloroquine ($p=0.033$).

Conclusion: The presence of RD did not affect the course of COVID-19 disease. Sulfasalazine had a negative effect on the course of COVID-19 disease, whereas CsA had a positive effect. The effect of CsA and SSZ on COVID-19 pneumonia needs to be evaluated with further studies.

Keywords: Rheumatic diseases, COVID-19, immunosuppressive drugs

Öz

Giriş: Bu çalışma, romatizmal hastalığı olan hastalarda Koronavirüs hastalığı-2019'un (COVID-19) seyrini belirlemeyi ve immünsüpresif (İS) ilaçların COVID-19 şiddeti üzerindeki etkilerini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Koronavirüs hastalığı-2019 nedeniyle hastaneye yatırılan 988'i kadın ve 917'si erkek, 57'si romatizmal hasta olmak üzere toplam 1,905 hastanın verileri geriye dönük olarak analiz edildi. İmmünsüpresif ilaçlar, demografik özellikler, komorbiditeler, COVID-19 tedavisinde kullanılan ilaçlar, laboratuvar ve toraks tomografi sonuçları, hastanede kalış süresi (HKS), yoğun bakım ünitesi (YBÜ) ve ölüm oranları romatizmal hastalar ile romatizmal olmayan hastalar arasında karşılaştırıldı. Ayrıca İS olan ve olmayan hastalar da karşılaştırıldı. Her bir İS ilacın pnömoni varlığı, HKS, YBÜ ve mortalite sıklığı ve kötü prognostik faktörler üzerindeki etkileri ayrıca değerlendirildi.

Bulgular: Pnömoni ($p=0,358$), HKS ($p=0,650$), YBÜ ($p=0,386$) ve ölüm oranları ($p=0,386$) romatolojik hasta ve romatolojik olmayan hastalarda benzer bulundu. Hastanede kalış süresi ($p=0,881$), YBÜ ($p=0,176$) ve mortalite oranları ($p=0,176$) İS alan ve almayan romatoloji hastaları arasında

Address for Correspondence/Yazışma Adresi: Selime ERMURAT MD, University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital, Clinic of Rheumatology, Bursa, Turkey

Phone: +90 505 544 67 83 E-mail: selimeermurat@hotmail.com ORCID ID: orcid.org/0000-0001-9945-8940

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farklı değildi. Sülfasalazin (SLZ) alan romatolojik hastalarda YBÜ ($p=0,003$) ve mortalite ($p=0,035$) oranları anlamlı olarak daha yüksekti. Siklosporin A (CsA) alan romatolojik hastalarda anlamlı olarak daha az pnömoni vardı ($p=0,040$). Siklosporin A ($p=0,022$) ve hidroksiklorokin alan romatolojik hastalarda C-reaktif protein düzeyi anlamlı olarak daha düşüktü ($p=0,033$).

Sonuç: Romatolojik hastalık varlığının COVID-19 hastalığının seyrini etkilemediği bulundu. Sülfasalazin, COVID-19 hastalığının seyrini olumsuz etkileyebilirken, CsA olumlu etkiliyor olabilir. Siklosporin A ve SLZ'nin COVID-19 pnömonisi üzerindeki etkisinin ileri çalışmaları değerlendirilmesi gerekmektedir.

Anahtar Kelimeler: Romatolojik hastalıklar, COVID-19, immünsüpresif ilaçlar

Introduction

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has progressed rapidly into a worldwide pandemic. The SARS-CoV-2 infection has a heterogenous disease course. It may be asymptomatic or cause only mild symptoms in the majority of the cases. However, it can drive profound immunological complications such as macrophage activation syndrome, resulting in cytokine storm syndrome and acute respiratory distress syndrome (ARDS) in some patients^[1]. The progression to ARDS in COVID-19 is associated with the manifestation of excessive release of inflammatory cytokines, especially interleukin (IL)-2, IL-6, IL-10, IL-12, and tumor necrosis factor- α ^[2]. It is believed that anti-inflammatory therapies may benefit the severely affected patients as hyperinflammation is the underlying factor of severe COVID-19. Some pathologies also cause rheumatic diseases (RDs) in the immune system, and anti-inflammatory drugs are used for the treatment of RDs^[3]. Recently, it has been reported that a few antirheumatic drugs, including chloroquine, hydroxychloroquine (HCO), JAK inhibitors, IL-6 and IL-1 inhibitors, glucocorticoids (GC), intravenous immunoglobulin (IVIG), and colchicine are used for the treatment of patients with mild or severe COVID-19^[2,3]. However, data on the susceptibility, disease severity, and prognosis of COVID-19 in patients with RDs on immunosuppressants is still lacking. More observation data about the prevalence and severity of COVID-19 in patients with RDs and experience managing such cases are needed.

This study aims to compare the course of COVID-19 in hospitalized rheumatic patients (RPs) and non-RPs, and to evaluate the effect of IS drugs used in COVID-19 patients with RDs on the course and severity of the disease.

Materials and Methods

Study Population and Design

Ethics committee approval was obtained from the Bursa Yüksek İhtisas Training and Research Hospital Ethics Committee, dated 24.06.2020 and numbered 2011-KAEK-25 2020/06-10. National permits were then obtained from the Bursa Provincial Public Health Directorate, which is included in the combat against the COVID-19 pandemic. Thus, all stages of the study complied with the Declaration of Helsinki.

Data Collection

Electronic files of 1,928 patients admitted to Bursa Yüksek İhtisas Training and Research Hospital with a diagnosis of COVID-19 between 16.03.2020 and 31.05.2020 were retrospectively analyzed. These patients were diagnosed with COVID-19 in line with the interim guidance^[4]. Positive polymerase chain reaction (PCR) tests were considered "definite" cases. Cases of negative PCR tests that were accompanied by symptoms such as fever, sore throat, shortness of breath, cough, loss of smell, low oxygen saturation, and "typical" radiographic results were accepted as a "possible" COVID-19 infection if there is no other reason to explain the symptoms^[5]. Peripheral, bilateral (multilobar), and multifocal round ground-glass opacities were considered "typical" radiographic results. Round or non-peripheral multifocal, diffuse, perihilar, or unilateral ground-glass opacities were considered "uncertain" radiological results^[4,6].

Demographic characteristics, comorbidities, IS drugs, laboratory results, thorax computed tomography (CT) results, drugs used in the treatment of COVID-19, duration of hospitalization (DOH) intensive care unit (ICU), and mortality rates of the patients were recorded.

Determination of Groups and Inclusion-exclusion Criteria

The patients were divided into two groups as RPs and non-RPs. Patients who were previously evaluated and diagnosed by a rheumatologist and whose International Classification of Diseases-10 diagnosis code was entered into the hospital system were included in the RPs group. Patients except RPs were determined as a non-rheumatological group. Patients under the age of 18, outpatients, patients with inaccessible data, cancer patients, and patients receiving IS drugs for any reason other than RDs were not included in the study.

Rheumatic Patients with and without Immunosuppressive Use

Rheumatic patients were divided into two groups as IS patients and non-IS patients. Glucocorticoids, methotrexate (MTX), leflunomide (LEF), sulfasalazine (SSZ), cyclosporine (CsA), azathioprine, tacrolimus (TAC), and/or biological agents were categorized as IS drugs. Patients taking these IS drugs were determined as IS patients. Hydroxychloroquine, colchicine, duloxetine, pregabalin, and/or non-steroidal anti-inflammatory

drugs (NSAIDs) were categorized as non-IS drugs. Patients using non-IS drugs were determined as non-IS patients. The presence of pneumonia, DOH, ICU, and mortality rates, and poor prognostic factors were evaluated and compared between RPs and non-RPs as well as between IS and non-IS patients. High C-reactive protein (CRP), lymphocyte, ferritin, and D-dimer were determined as poor prognostic factors under the COVID-19 interim treatment guidelines^[7].

Statistical Analysis

The data analysis was performed using IBM Statistical Package for the Social Sciences 21.0 statistics package software. Whether the data were normally distributed was evaluated by Kolmogorov-Smirnov or Shapiro-Wilk tests. The Student's t-test was used for continuous variables with normal distribution, and the Mann-Whitney U test was used for continuous variables without normal distribution. Chi-square (χ^2) test or Fisher's exact test was used to compare qualitative variables between groups. The relationship of quantitative variables with each other was evaluated by Spearman's correlation analysis. P value <0.05 was considered statistically significant.

Results

A total of 1,905 patients who met the criteria among 1,928 patients hospitalized with a diagnosis of COVID-19 were included in the study. Fifty seven of whom were diagnosed with RD. The mean age of the patients included in the study was 51.18 ± 21.24 years, and 59.9% were female. The mean age of RPs was 57.72 ± 16.53 years, and 80.4% of RPs were female. The distribution of accompanying RDs in the RPs group is shown in Figure 1. The distribution of RDs was as follows: rheumatoid arthritis, 40.4% (n=23); ankylosing spondylitis, 10.5% (n=6); familial Mediterranean fever (FMF), 8.8% (n=5); Sjögren's syndrome, 8.8% (n=5); systemic lupus erythematosus (SLE), 8.8% (n=5); Behçet's disease, 5.3% (n=3); psoriatic arthritis (PSA), 5.3% (n=3); systemic sclerosis, 3.5% (n=2); polymyalgia rheumatica, 3.5% (n=2); fibromyalgia, 3.5% (n=2); and gout, 1.8% (n=1).

Comparison of COVID-19 Patients with and without Rheumatic Disease

Comparison of demographic characteristics, comorbidities, drugs, and outcomes between RPs and non-RPs hospitalized for SARS-CoV-2 infection is shown in Table 1. The gender distribution was found to be different between the groups ($p < 0.001$) even though the median age was not different ($p = 0.071$). The percentage of females was higher in patients with RPs (84.2% vs 50.9%). The presence of comorbidities including diabetes mellitus, hypertension, chronic heart failure, and chronic renal failure was significantly high in patients with RDs ($p = 0.032$, $p < 0.001$, $p < 0.001$, $p = 0.001$, respectively).

Figure 1. Distribution of rheumatological diseases

RA: Rheumatoid arthritis, AS: Ankylosing spondylitis, FMF: Familial Mediterranean fever, SSC: Systemic sclerosis, PMR: Polymyalgia rheumatica, SLE: Systemic lupus erythematosus, FMS: Fibromyalgia syndrome, PSA: Psoriatic arthritis

The frequency of pneumonia and outcome parameters were similar in both groups. The frequency of each drug used in the treatment of COVID-19 and the outcomes parameters were not different between the groups.

Comparison of COVID-19 Patients with and without Immunosuppressive Drugs

The comparison of demographic data, comorbidities, COVID-19 treatments, and outcome parameters in RPs with and without IS drugs are shown in Table 2. Among the RPs, 70.2% (n=40) of them were receiving at least one IS drug. There was no significant difference between the age, gender distribution, comorbidities, laboratory and radiological results, and the drugs used in the treatment of COVID-19 between IS and non-IS patients. In addition, there was no difference between the groups in terms of DOH ($p = 0.881$), ICU ($p = 0.176$), and mortality rates ($p = 0.176$).

P values showing the effect of antirheumatic drugs on poor prognostic factors are shown in Table 3. There was no significant effect of GC, NSAIDs, MTX, LEF, colchicine, and TAC on poor prognostic factors. Intensive care unit and mortality rates were higher in patients receiving SSZ than those who did not ($p = 0.003$, $p = 0.035$, respectively). Intensive care unit and mortality rates were 40% in patients receiving SSZ whereas 3.8% in patients not receiving SSZ. It was found that patients receiving CsA had significantly less pneumonia ($p = 0.040$), and CRP was significantly lower in patients receiving CsA ($p = 0.022$). The frequency of pneumonia on CT was 25% in patients

Table 1. Comparison of demographic characteristics, comorbidities, drugs, and outcomes between patients with and without rheumatic disease hospitalized for COVID-19 infection

	Patients with rheumatic disease (n=57)	Patients without rheumatic disease (n=1848)	p
Age, years, median (min-max)	57 (20-91)	54 (18-99)	0.071
Female, n (%)	48 (84.2)	940 (50.9)	<0.001
Comorbidities, n (%)			
Diabetes mellitus	13 (22.80)	240 (12.98)	0.032
Hypertension	29 (50.87)	418 (22.62)	0.000
Cardiovascular disease	9 (15.78)	64 (3.46)	<0.001
Chronic renal failure	6 (10.52)	38 (2.05)	0.001
Pneumonia by CT, n (%)	34 (59.64)	880 (47.61)	0.358
COVID-19 medication, n (%)			
Hydroxychloroquine	57 (100)	1838 (99.45)	0.833
Oseltamivir	30 (52.63)	888 (48.05)	0.317
Azithromycin	35 (61.40)	1186 (64.17)	0.367
Low molecular weight heparin	40 (70.17)	1097 (59.36)	0.065
Favipiravir	7 (12.28)	215 (11.6)	0.512
Tocilizumab	0 (0)	8 (0.43)	0.782
Outcome			
TOH, day, median (min-max)	5 (1-21)	5 (1-59)	0.650
TOH, day, n (%)			0.880
<10 days	48 (84.2)	1595 (86.7)	
11-20 days	8 (14)	207 (11.2)	
21-30 days	1 (1.8)	30 (1.6)	
>30 days	0 (0)	8 (0.4)	
ICU, n (%)	4 (7.01)	101 (5.4)	0.386
Mortality rate, n (%)	4 (7.01)	106 (5.73)	0.568

TOH: Time of hospitalization, ICU: Intensive care unit, min-max: Minimum-maximum, CT: Computed tomography, COVID-19: Coronavirus disease-2019

receiving CsA whereas 65.3% in patients not receiving CsA. Median CRP was 5.7 (3.14-15.3) mg/L in patients receiving CsA and 21.4 (3.11-183) mg/L in those who did not receive CsA. The median CRP was significantly high in patients receiving HCQ ($p=0.033$); CRP was 45.1 (3.11-163) mg/L in patients receiving HCQ whereas it was 14 (3.11-183) in patients not receiving HCQ.

Mortality in Rheumatic Patients

Mortality rate in patients with RDs was 7% ($n=4$). The mean age of the RPs who died was 65.25 ± 18.5 years. Three of four RPs were male. Three of the patients were diagnosed with RA; they all received IS drugs, and all of them had multiple

Table 2. The comparison of demographic data, comorbidities, COVID-19 treatments, and outcome parameters in rheumatic disease patients receiving and not receiving immunosuppressive drugs

	Patients receiving IS drugs (n=40)	Patients not receiving IS drugs (n=17)	p value
Age, years, mean $\pm$ SD	58.8 $\pm$ 15.85	55 $\pm$ 18.23	0.553
Female, n (%)	35 (87.5)	13 (76.5)	0.252
Comorbidities, n (%)			
Diabetes mellitus	8 (20)	5 (29.41)	0.327
Hypertension	23 (57.5)	6 (35.29)	0.106
COPD	6 (15)	2 (11.76)	0.554
Cardiovascular disease	8 (20)	1 (5.88)	0.176
Chronic renal failure	4 (10)	2 (11.76)	0.527
Acute phase reactants			
ESR, mm/h, mean $\pm$ SD	54.23 $\pm$ 25.56	48.14 $\pm$ 26.00	0.991
CRP, mg/L, median	18.3 (3.11-183)	16.8 (3.11-177)	0.782
CBC mean $\pm$ SD			
WBC, 10 ³ cells/ μ l	6.45 $\pm$ 3.25	6.29 $\pm$ 2.17	0.164
Lym, 10 ³ cells/ μ l	1.67 $\pm$ 0.57	1.56 $\pm$ 0.62	0.190
Hb, g/dl	11.55 $\pm$ 1.89	12.12 $\pm$ 1.40	0.201
PLT, 10 ³ cells/ μ l	234 $\pm$ 90	248 $\pm$ 72	0.302
Biochemical and hormonal parameters, median (min-max)			
Ferritin, ng/ml	110 (16-370)	70.88 (19-496)	0.327
Creatinine, mg/dl	0.69 (0.27-7.04)	0.9 (0.41-1.59)	0.441
D-dimer, μ g/ml	0.64 (0.19-5.36)	0.82 (0.30-2.47)	0.487
Troponin, pg/ml	4.55 (3-335)	3.68 (3-23.47)	0.645
Fibrinogen, mg/dl	397 (181-900)	466 (138-900)	0.840
Pneumonia by CT, n (%)	25 (62.5)	9 (52.94)	0.351
COVID-19 medication, n (%)			
Hydroxychloroquine	40 (100)	17 (100)	1.000
Oseltamivir	19 (47.5)	11 (64.70)	0.184
Azithromycin	25 (62.5)	10 (58.82)	0.511
Low molecular weight heparin	28 (70)	12 (70.59)	0.613
Favipiravir	4 (10)	3 (17.64)	0.344
Parameters of outcome			
DOH, day, median (min-max)	5 (1-19)	5 (1-21)	0.881
DOH, day, n (%)			0.293
<10 days	34 (85)	14 (82.35)	
11-20 days	6 (15)	2 (11.76)	
21-30 days	0 (0)	1 (5.8)	
ICU, n (%)	4 (10)	0 (0)	0.176
Mortality rate, n (%)	4 (10)	0 (0)	0.176

COVID-19: Coronavirus disease-2019, IS: Immunosuppressive, COPD: Chronic obstructive pulmonary disease, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, CBC: Complete blood count, WBC: White blood cell, Lym: Lymphocyte, Hb: Hemoglobin, PLT: Platelet, DOH: Duration of hospitalization, ICU: Intensive care unit, SD: Standard deviation, CT: Computed tomography, min-max: Minimum-maximum

Table 3. P values showing the effect of antirheumatic drugs on poor prognostic factors

	<i>Pneumonia</i>	<i>CRP</i>	<i>Lym</i>	<i>Ferritin</i>	<i>D-dimer</i>	<i>DOH</i>	<i>ICU</i>	<i>Mortality</i>
Glucocorticoids, (n=22)	0.407	0.070	0.718	0.406	0.817	0.868	0.121	0.155
Hydroxychloroquine, (n=17)	0.140	0.033 ¹	0.179	0.883	0.886	0.525	0.827	0.827
Colchicine, (n=10)	0.287	0.915	0.867	0.316	0.201	0.274	0.684	0.548
Methotrexate, (n=14)	0.124	0.080	0.718	0.968	0.588	0.297	0.220	0.250
Leflunomide, (n=6)	0.208	0.853	0.435	0.851	0.726	0.286	0.477	0.477
Sulfasalazine, (n=5)	0.074	0.189	0.594	0.242	0.059	1.000	0.003 ²	0.035 ²
Cyclosporine, (n=8)	0.040 ³	0.022 ³	0.190	0.661	0.120	0.569	0.402	0.536
Tacrolimus, (n=1)	0.404	0.114	0.101	0.916	0.844	0.580	0.782	0.930
Azathioprine, (n=1)	0.220	0.780	0.301	–*	–*	0.103	0.782	0.782
TNF inhibitors, (n=1)	0.227	0.663	0.377	0.346	0.227	0.602	0.786	0.786
NSAID, (n=5)	0.074	0.342	0.413	0.260	0.493	0.179	0.315	0.315

¹Lower CRP was seen in patients receiving hydroxychloroquine.

²Intensive care units and mortality rates were more frequent in patients receiving sulfasalazine.

³Less pneumonia and lower CRP were seen in patients receiving cyclosporine.

*The p value could not be calculated since the ferritin and fibrinogen levels of the only patient receiving azathioprine were not calculated.

Lym: Lymphocyte count, DOH: Duration of hospitalization, ICU: Intensive care unit, CRP: C-reactive protein, TNF: Tumor necrosis factor, NSAID: Non-steroidal anti-inflammatory drugs

comorbidities. Another patient's diagnosis was FMF; she was receiving colchicine and had no accompanying comorbidity.

Discussion

It was noted in this study that hospitalized COVID-19 patients with RDs had more comorbidity compared to non-RPs. However, the outcomes such as DOH, ICU, and mortality rates were not different between RPs and non-RPs. In addition, antirheumatic drugs did not affect the course of COVID-19 nor the outcomes except CsA and SSZ; the disease progressed better in patients receiving CsA but worse in patients receiving SSZ in our study.

Patients with RDs who received IS therapy required special attention as they became more susceptible to viral and bacterial infections. However, a higher incidence of COVID-19 had not been demonstrated in patients with RDs so far, even if they received biological Disease-Modifying Antirheumatic Drugs (DMARDs) compared with the general population^[8-10]. In addition, it has been reported that patients treated with DMARDs and infected with COVID-19 do not develop life-threatening complications due to underlying drugs^[11]. Data of 600 patients in the COVID-19 Global Rheumatology Alliance registry showed similar results. In addition, most conventional synthetic DMARDs (csDMARDs) have not been associated with worse outcomes^[12]. Methotrexate and LEF as DMARDs in the treatment of RDs may also exert a protective effect against COVID-19^[13]. Patients with SLE and vasculitis showed a higher tendency to be hospitalized than other patients; however, the main factor was the prednisolone dose at 10 mg/day. It was not associated with DMARD treatment^[13,14]. In our study, no effects were observed in severity and the poor prognostic factors in COVID-19 according to the type of rheumatologic disease.

It is thought that some antirheumatic drugs could be used for prevention and treatment in COVID-19 patients^[15]. These include antimalarials, colchicine, GCs, JAK inhibitors, IL-6 or IL-1 antagonists, and IVIG; however, they are used to treat COVID-19 in clinical studies on weak evidence^[16-18]. Furthermore, these drugs also carry a risk for viral infections. Therefore, it is still a matter of curiosity regarding whether their chronic use in RPs may change the course of COVID-19 or may be used to treat severe COVID-19 cases.

The effects of antirheumatic drugs on COVID-19 were examined in this study. Only two antirheumatic drugs affected the prognosis of the course of COVID-19. One of them was SSZ; increased ICU and mortality rates were found in patients receiving SSZ. The other antirheumatic drug was CsA, and it was observed that patients receiving CsA had less pneumonia and lower CRP. There is no study in the literature showing the effect of SSZ on the course of COVID-19. The only report on SSZ in patients with COVID-19 is that DRESS syndrome developed due to COVID-19 in a patient receiving SSZ due to ulcerative colitis^[19]. Cyclosporine can be used in the treatments of Behçet's disease, psoriatic arthritis, and lupus nephritis in rheumatology. Cyclosporine is a polypeptide immunosuppressant agent that suppresses T cell responses by preventing the transcription of genes encoding IL-2. The primary molecular target of CsA is cyclophilin, a specific cytosolic-binding protein that many viruses require for replication. Therefore, it has been suggested that there may be a possible beneficial effect in patients receiving CsA during COVID-19, and many studies have supported these results^[20-22]. Cyclosporine administered in addition to steroid therapy to COVID-19 patients was shown to improve the course of the disease and reduce mortality,

especially in those with moderate to severe disease in a study by Gálvez-Romero et al.^[23]. Schuurmans and Hage^[24] reported that CsA reduced mortality significantly in COVID-19 patients, resulting in an impressive survival curve significantly different compared to all other treatments. Treatment with CsA leads to a decrease in hyperinflammation and probably to a decreased viral replication^[25]. Cour et al.^[26] reported that CsA could prevent uncontrolled inflammatory response, SARS-CoV-2 replication, and acute lung injury. In addition, it was emphasized that CsA is a valid candidate to treat COVID-19 patients with acute respiratory failure. The Immunonephrology Working Group of the European Renal Association-European Dialysis and Transplant Association recommendations include a recent comment that CsA may be the drug of choice during the COVID-19 pandemic for kidney transplant^[27-29]. Our study is also important to support the positive effect of CsA on the course of COVID-19, and it suggests that it can be used in the treatment of COVID-19, similar to the other studies.

Hydroxychloroquine was presented as both a preventive and therapeutic treatment for COVID-19 at the onset of the pandemic, but it was shown to be of no benefit in later clinical studies^[30,31]. It was shown in this study that the clinical course of the patients who were receiving HCQ before the COVID-19 was not better, and it had no protective effect. Moreover, CRP was higher in patients receiving HCQ in our study. Other studies are investigating the clinical effects of colchicine in COVID-19^[32]. Scarsi et al.^[33] expressed that colchicine may be used in hospitalized patients with COVID-19 pneumonia and ARDS thanks to its well-known anti-inflammatory and potential antiviral properties. Patients treated with colchicine had a better survival rate in this study. A recent study demonstrated that colchicine delays the time to clinical deterioration in COVID-19^[34]. Ten patients were receiving colchicine before they were diagnosed with COVID-19 in our study. No difference was found between patients with RDs receiving or not receiving colchicine. In our study, the IL-6 inhibitor tocilizumab (TOC) was used in eight patients with a severe infection. Six patients who received TOC survived the severe infection of COVID-19, but two of them died. No patients were receiving IL-1 antagonists or JAK inhibitors for treatment since our study included patients in the early stages of the pandemic. No positive or negative effects were observed in the clinical course of patients receiving MTX, LEF, TAC, GC, and NSAIDs.

Comorbidities were significantly higher in RPs compared to the non-RPs in our study, similar to other studies^[13]. In our study, more comorbid diseases were observed in patients with RDs; however, mortality rates or poor prognostic factors did not increase^[35]. It was also supported that IS drugs did not worsen the course of COVID-19 despite concomitant diseases. Therefore,

it is thought that having RDs or receiving IS drugs may have a protective effect on COVID-19.

The most important limitation of our study is that it is a short-term retrospective single-center study, and it includes patients admitted in the early period of the pandemic. However, it has been useful in determining how COVID-19 infection behaves in RPs and which risk factors are associated with a detrimental prognosis. Finally, this study may also provide some evidence on the use of antirheumatic drugs during the COVID-19 pandemic.

Conclusion

We found that RPs did not have a higher risk for infection and did not increase the severity of COVID-19 as suggested in previous studies and IS drugs except SSZ did not adversely affect the course of the disease. A significant increase in the frequency of ICU and mortality rates in patients receiving SSZ was reported. Less pneumonia and lower CRP were significantly observed in patients receiving CsA. Therefore, it is thought that CsA could positively affect the course of the disease and could be used to treat COVID-19 pneumonia in case of hyperinflammation.

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Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Bursa Yüksek İhtisas Training and Research Hospital Ethics Committee, dated 24.06.2020 and numbered 2011-KAEK-25 2020/06-10.

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: K.A., Concept: S.E., Design: S.E., K.A., Data Collection or Processing: S.E., S.A., V.G., Analysis or Interpretation: S.E., K.A., Literature Search: S.E., S.A., V.G., Writing: S.E., K.A.

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