Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:171-179
DOI: 10.4274/BMJ.galenos.2023.2022.5-9

Research

Effects of the COVID-19 Pandemic in Unvaccinated Rheumatoid Arthritis, Ankylosing Spondylitis, and Psoriatic Arthritis Patients Using Disease-modifying Antirheumatic Drugs

Romatizmal Hastalık Nedeniyle Hastalığı Modifiye Edici Antiromatizmal İlaç Kullanan Hastaların COVİD-19 Pandemisi Dönemindeki Sağlık Durumları

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ABSTRACT

Objective: To investigate the health status, experiences, and status of contracting or being affected poorly by coronavirus disease-2019 (COVID-19) in patients using disease-modifying antirheumatic drugs (DMARD).

Methods: Patients using DMARD for rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis registered in our rheumatic diseases outpatient clinic were assessed during their routine follow-up control between July 2020 and January 2021. Their health status between March and June 2020 was also registered in the first evaluation. A follow-up form was used in which demographic data, systemic diseases and drugs, rheumatic diseases and treatments, and changes in treatment and complaints during the pandemic period were questioned.

Results: One hundred fifty six (95 female, 61 male) patients were included in the study, the mean age was 43.4. There was no relationship between age, gender, body mass index, occupation, rheumatic disease group, and DMARD groups, with conditions of getting or being affected severely by COVID-19. Statistically significant relationships were found between having a chronic respiratory disease or having more than one comorbid disease and severe COVID-19 outcomes and between having moderate/high rheumatic disease activity and contracting COVID-19 ($p<0.05$ for all). The rate of getting COVID-19 in smokers was significantly lower than in non-smokers ($p=0.039$). There was a significant increase in disease activity during the pandemic period compared with the pre-pandemic period ($p<0.001$). A statistically significant relationship was found between making changes for treating rheumatic disease and an increase in disease activity ($p=0.003$).

Conclusion: Those with multiple comorbid diseases have an increased risk of severe COVID-19, and those with moderate- tohigh disease activity have an increased risk of developing COVID-19. The decrease in compliance with routine follow-up and drug treatment during the pandemic increases the risk of increased rheumatic disease activity.

Keywords: Biologic drugs, COVID-19, DMARD, hydroxychloroquine

ÖZ

Amaç: Romatizmal hastalıkları nedeniyle hastalığı modifiye edici antiromatizmal ilaç (DMARD) kullanan hastaların koronavirüs hastalığı-2019 (COVİD-19) pandemisi döneminde sağlık durumlarını, romatizmal hastalıkları ve DMARD kullanımları açısından deneyimlerini ve COVİD-19'a yakalanma/ağır geçirme durumlarını araştırmaktır.

Gereç ve Yöntem: Romatizmal hastalıklar polikliniğimizde takipli olan ve tedavisinde DMARD kullanan romatoid artrit, ankilozan spondilit ve psöriatik artrit hastaları Haziran 2020-Ocak 2021 arasında rutin takipleri sırasında değerlendirildi. Hastaların demografik verileri, sistemik hastalıkları ve ilaçları, romatizmal hastalıkları ve tedavileri, tedavide ve şikayetlerdeki değişimleri bir takip formu kullanılarak kaydedildi.

Bulgular: Çalışmaya dahil edilen 156 (95 kadın, 61 erkek) hastanın yaş ortalaması 43,4'tü. Hastaların %25'i randevularına düzenli gelirken, %67'si tedavisinde değişiklik yapmamıştı. Yaş, cinsiyet, vücut kitle indeksi, meslek, romatizmal hastalık grubu ve DMARD grupları ile COVİD-

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Cite as: Sarı K, Ünlü Özkan F, Aktaş İ, Akpınar P. Effects of the COVID-19 Pandemic in Unvaccinated Rheumatoid Arthritis, Ankylosing Spondylitis, and Psoriatic Arthritis Patients Using Disease-modifying Antirheumatic Drugs. Med J Bakirkoy 2023;19:171-179

Received: 22.05.2022
Accepted: 04.04.2023

19'a yakalanma/ağır geçirme durumları arasında ilişki saptanmadı. Bir kronik respiratuvar hastalığa sahip olma veya birden fazla komorbid hastalığa sahip olma ile COVİD-19'u ağır geçirme arasındaki ilişki istatistiksel olarak anlamlıydı (hepsi için p<0,05). Romatizmal hastalık aktivitesi orta/yüksek olanlarda, hastalık aktivitesi düşük/remisyonda olanlara göre COVİD-19'a yakalanma oranı anlamlı olarak daha yüksekti (hepsi için p<0,05). Sigara içenlerde COVİD-19'a yakalanma oranı, içmeyenlere göre anlamlı olarak daha düşüktü (p=0,039). Hastaların pandemi öncesine göre pandemi döneminde hastalık aktivitesinde anlamlı bir artış görüldü (p<0,001). Bu süreçte romatizmal hastalığının tedavisinde değişiklik yapma ile hastalık aktivitesinde artış durumu arasında istatistiksel olarak anlamlı bir ilişki bulundu (p=0,003).

Sonuç: Komorbid hastalıkları olanlarda COVİD-19'u ağır geçirme riski ve hastalık aktivitesi orta-yüksek olanlarda COVİD-19'a yakalanma riski artmıştır. Pandemi sürecinde rutin takibe ve ilaç tedavisine uyumun azalması, romatizmal hastalık aktivitesinde artış riskini artırmaktadır.

Anahtar Kelimeler: Biyolojik ilaçlar, COVİD-19, DMARD, hidroksiklorokin

INTRODUCTION

Inflammatory rheumatic diseases cause a predisposition to routine and opportunistic infections due to disease-related factors and immunosuppressive drugs used in the treatment (1). For this reason, both patients and doctors wondered whether inflammatory rheumatic diseases and immunosuppressive drugs used in the treatment increase the risk of getting or being severely affected by coronavirus disease-2019 (COVID-19). In the first period of the epidemic, patients tended to discontinue their immunosuppressive treatments due to the risk of contracting COVID-19 and the fear of severe illness, and they believed that stopping the treatment would reduce this risk (2-4). In addition, the risk of infection increases as the severity of rheumatic disease increases (5,6).

During the COVID-19 pandemic, conflicting results have been published regarding the risk of getting or being affected severely by COVID-19 for those with rheumatic diseases. There are studies reporting an increased risk of hospitalization and death due to COVID-19 in certain rheumatic disease groups or those using certain immunosuppressive drugs (7-9). On the other hand, some studies state that there is no increase in the risk of getting COVID-19 infection or severe course in rheumatic disease patients compared with the healthy population (10,11). The risk of hospitalization due to COVID-19 was associated with age, presence of comorbid diseases, and high prednisone dose (≥10 mg/day) in patients with rheumatic diseases (12). According to the results of studies evaluating the relationship between the use of disease-modifying antirheumatic drugs (DMARD) and poor outcomes of COVID-19, conventional synthetic DMARD (csDMARD), biological DMARD (bDMARD), and targeted synthetic DMARD (tsDMARD) groups are not associated with high risk; however, specific drugs such as sulfasalazine (SSZ), rituximab (RTX), and Janus kinase inhibitors may be associated with adverse outcomes (9,13,14). In this study, we evaluated the patients followed up in our rheumatic diseases outpatient clinic between July 2020 and January 2021, recorded their health status between March 2020 and January 2021, and questioned them again at each examination. This study aimed to investigate the health status of patients using DMARD for rheumatic diseases during the COVID-19 pandemic and to evaluate the relationship between demographic data, rheumatic disease, and DMARD use and COVID-19-related outcomes.

METHODS

We obtained the Clinical Research Ethics Committee approval from University of Health Sciences Türkiye, İstanbul Fatih Sultan Mehmet Training and Research Hospital (no: FSM EAH-KAEK 2020/95, date: 09.07.2020) for this study. Among the patients followed up in our rheumatic diseases outpatient clinic with the diagnosis of rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA), those older than 18 years of age, using DMARD for treatment, and volunteering to participate were included. Those under the age of 18 years and individuals who refused to participate were not included Exclusion criteria were being under 18 years of age and not agreeing to participate in the study. Written informed consent was obtained from all participants.

We used a follow-up form to evaluate the health status of the patients. In this form; age, gender, height, weight, smoking status (active smoker/ex-smoker/never smoker), systemic diseases, rheumatic disease type and treatment, COVID-19-related conditions [reason for polymerase chain reaction (PCR) test if performed, computed tomography (CT) result if taken, COVID-19 treatment if received], COVID-19 risk perceptions (with Likert scale), routine follow-up and treatment compliance, changes in the complaints of those who made changes in rheumatic disease treatment, and rheumatic disease activity (last control before the pandemic and the first control during the pandemic period) were recorded. Conditions associated with COVID-19, including March-June 2020, were recorded at the initial evaluation and were re-questioned at each subsequent follow-up, and recorded if there was a change in the patient's status. When comparing the data, we divided the patients into two groups in terms of getting or not getting

COVID-19 and into three groups in terms of COVID severity as not infected, mild, or severe illness. The presence of pneumonia (confirmed by CT) or the hospitalization need, as accepted by the American College of Rheumatology, was determined as criteria for severe COVID-19 (15). According to this; cases with CT-confirmed pneumonia or requiring hospitalization for treating COVID-19 were classified as severe COVID-19. Cases with neither of these two conditions (i.e. confirmed by PCR only and treated at home) were classified as mild COVID-19. In the comparison of DMARD groups, we evaluated patients in three groups as csDMARD (monotherapy or combinations), b/tsDMARD, and combined DMARD (csDMARD + b/tsDMARD) users. In terms of rheumatic disease diagnoses, comparisons were made as RA, AS, and PsA groups separately and as RA and spondyloarthritis (SpA) (AS and PsA) groups.

Statistical Analysis

Categorical variables were summarized with frequencies and percentages. Numerical variables were summarized with mean and standard deviation or median and quartiles according to their distribution. The distribution of numerical variables was evaluated using the Kolmogorov-Smirnov test. Comparisons of numerical variables between dual COVID groups (getting/not getting) were made using t-test or Mann-Whitney U test according to their distribution. Comparisons of numerical variables between triple COVID groups (did not get/mild/severe) were made by ANOVA or Kruskal-Wallis test, according to their distribution. The relationship between categorical variables was examined using the chi-square test. The McNemar test was used to compare the disease activities before and during pandemics. $P<0.05$ was considered statistically significant. The R version 4.0.4 (2021-02-15) program was used for statistical analysis.

RESULTS

Patient Characteristics and Comorbid Diseases

A total of 156 patients (95 female, 61 male) were included in the study. The mean age of the patients was 43.4. Since vaccination did not start in our country at that time, none of the patients were vaccinated for COVID-19. The most common comorbid diseases in patients were hypertension (27.6%), diabetes mellitus (14.1%), cardiovascular diseases (15.4%), and chronic respiratory diseases (CRD) (15.4%), and others were hypothyroidism (n=17), chronic renal failure (n=2), focal nodular hyperplasia of the liver (n=2), familial Mediterranean fever (n=2), and benign prostatic hyperplasia (n=2). When we grouped the patients according to the number of comorbidities, we found that the rate of those with zero, one, and more than one comorbid disease was 57%, 26.9%, and 15.4%, respectively. Age, gender, body mass index (BMI), smoking status, comorbid diseases, and COVID-19 results are presented in Table 1.

No statistically significant relationship was found between age, gender, BMI, and occupational status of patients and COVID-19 or COVID-19 severity ($p>0.05$ for all). There was a significant association between smoking status and not getting COVID-19 ($p=0.039$). Those who had COVID-19 had a lower smoking rate than those who had never had COVID-19 (16.7% and 42.4%, respectively). No significant association was found between getting COVID-19 and any comorbid disease or the number of comorbid diseases ($p>0.05$ for all). A statistically significant correlation was found between having severe COVID-19 and having CRD ($p<0.05$). The relationship between the number of comorbid diseases and severe COVID-19 was also statistically significant ($p<0.05$).

Rheumatic Diseases and DMARD Treatments

The rheumatic disease diagnoses of the patients were RA in 71 (45.5%), AS in 71 (45.4%), and PsA in 14 (9%). Diagnoses of rheumatic diseases, DMARD used in treatment, and COVID-19 status are given in Table 2.

No significant relationship was found between the diagnosis and duration of rheumatic disease and the severity of COVID-19 or COVID-19 ($p>0.05$ for all). There were no statistically significant differences between the DMARD groups in terms of getting COVID-19 or COVID-19 severity ($p>0.05$ for all). Although not statistically significant ($p=0.078$), the relationship between leflunomide use and COVID-19 severity was closer than for other csDMARDs.

Characteristics of Patients with COVID-19

Of the 156 patients included, 24 (23 with a positive PCR result and 1 with typical findings seen on thorax CT although the PCR result was negative) were diagnosed with COVID-19. Of the 24 patients diagnosed with COVID-19, 16 were treated with mild symptoms, while 8 had severe COVID-19 findings [pneumonia/hospitalization and need for oxygenation/intensive care unit (ICU)]. One patient with severe disease symptoms required ICU admission and intubation, but was subsequently extubated, and discharged with recovery. None of the patients died. Demographic data, rheumatic disease diagnoses, DMARD treatments, PCR and CT findings, and treatments for COVID-19 in patients with COVID-19 are listed in Table 3.

COVID-19 Risk Perceptions and Adherence to Follow-up and Treatment

COVID-19 risk perceptions of patients, depending on their rheumatic diseases and the DMARD they use, are presented

Table 1. Demographic data, smoking status, comorbid diseases, and COVID-19 results

	COVID-19 situation							
	Getting COVID-19			COVID-19 severity				
	Yes (n=24)	No (n=132)	p	Mild (n=16)	Severe (n=8)	Did not get (n=132)	Total (n=156)	p
Age								
Mean ± SD	49.5±11.82	49.36±13.09	0.908[1]	46.06±10.79	56.38±11.34	49.36±13.09	49.39±12.87	0.159[2]
Gender								
Male	6 (25%)	55 (41.7%)	0.124[3]	5 (31.2%)	1 (12.5%)	55 (41.7%)	61 (39.1%)	0.206[3]
Female	18 (75%)	77 (58.3%)		11 (68.8%)	7 (87.5%)	77 (58.3%)	95 (60.9%)	
BMI (kg/m²)								
Mean ± SD	28.98±5.99	28.69±5.43	0.928[1]	27.89±4.73	31.15±7.87	28.69±5.43	28.74±5.50	0.783[2]
Smoking								
Active	4 (16.7%)	56 (42.4%)	0.039[3]	2 (12.5%)	2 (25%)	56 (42.4%)	60 (38.5%)	0.063[3]
Ex	4 (16.7%)	22 (16.7%)		4 (25%)	0	22 (16.7%)	26 (16.7%)	
Never	16 (66.7%)	54 (40.9%)		10 (62.5%)	6 (75%)	54 (40.9%)	70 (44.9%)	
Comorbidity								
HT	7 (29.2%)	36 (27.3%)	0.266[3]	3 (18.8%)	4 (50%)	36 (27.3%)	43 (27.6%)	0.266[3]
DM	2 (8.3%)	20 (15.2%)	0.621[3]	1 (6.2%)	1 (12.5%)	20 (15.2%)	22 (14.1%)	0.621[3]
CVD	8 (33.3%)	19 (14.4%)	0.201[3]	2(12.5%)	3 (37.5%)	19 (14.4%)	24 (15.4%)	0.201[3]
CLD	5 (20.8%)	8 (6.1%)	0.05[3]	1 (6.2%)	3 (37.5%)	8 (6.1%)	24 (15.4%)	0.005[3]
Number of comorbidities								
0	10 (41.7%)	80 (60.6%)	0.075[3]	9 (56.2%)	1 (12.5%)	80 (60.6%)	90 (57.7%)	0.018[3]
1	11 (45.8%)	31 (23.5%)		7 (43.8%)	4 (50%)	31 (23.5%)	42 (26.9%)	
>1	3 (12.5%)	21 (15.9%)		0	3 (37.5%)	21 (15.9%)	24 (15.4%)	

[1]Student's t-test; [2]ANOVA; [3]Chi-square
SD: Standard deviation, COVID-19: Coronavirus disease-2019, BMI: Body mass index, HT: Hypertension, DM: Diabetes mellitus, CVD: Cardiovascular diseases, CLD: Chronic lung diseases

in Figure 1. Accordingly, 70.5% of the patients thought that they were in the risk group for COVID-19 because of their rheumatic disease and 53% because of the DMARD they used in the treatment.

Only 39 (25%) of the patients had come to their follow-up regularly during this period. Reasons for not attending were as follows; no complaints (13.7%), hesitation to come to the hospital (58.1%), and reaching the doctor by phone (43.6%). Forty-two (26.9%) of the patients made changes for treating their rheumatic disease on their own, 8 (5.1%) made a temporary change in the treatment, and then continued as before.

As expected, those who made changes in their rheumatic disease treatment were more likely to have increased rheumatic disease activity than those who did not change their treatment. An increase in rheumatic disease activity was observed in 52% of patients who changed their treatment, this rate was 27.4% in patients who continued their treatment with the same regimen, and this was statistically significant (p=0.003). Adherence to DMARD treatment was higher in the RA group than in the SpA group. The rates of continuing routine treatment were 83.1% in the RA group and 55.3% in the SpA group, which was statistically significant (p=0.001).

Rheumatic Disease Activities and COVID-19 Outcomes

When the rheumatic disease activities (Disease Activity score-28 for RA, Bath Ankylosing Spondylitis Disease Activity index for AS, Disease Activity in Psoriatic Arthritis for PsA) of the patients before and during the pandemic period (Table 4) were compared, an increase in disease activity was observed in 55 patients. Disease activity changes between the first evaluation during the pandemic period and the last evaluation before the pandemic were significant (p<0.001). It was observed that patients in remission progressed to low and moderate disease activity groups, and patients with low disease activity progressed to high disease activity groups.

When patients with rheumatic disease activity in remission or low were compared with patients with moderate or high activity (Table 5); a statistically significant relationship was found between having moderate or high rheumatic disease activity and getting COVID-19, but not in terms of COVID-19 severity.

DISCUSSION

In this study, we evaluated patients using DMARD for rheumatic diseases in terms of the relationship between demographic and clinical characteristics and COVID-19 or

Table 2. Diagnoses, DMARD treatments and COVID-19 results

	COVID-19 situation							
	Getting COVID-19			COVID-19 severity				
	Yes (n=24)	No (n=132)	p	Mild (n=16)	Severe (n=8)	Did not get (n=132)	Total (n=156)	p
Disease								
RA	14 (58.3%)	57 (43.2%)	0.340[1]	8 (50.0%)	6 (75.0%)	57 (43.2%)	71 (45.5%)	0.473[1]
AS	9 (37.5%)	62 (47.0%)		7 (43.8%)	2 (25.0%)	62 (47.0%)	71 (45.5%)	
PsA	1 (4.2%)	13 (9.8%)		1 (6.2%)	0	13 (9.8%)	14 (9.0%)	
Disease duration Mean ± SD	116.92±84.94	125.27±72.62	0.764[2]	123.88±91.9	103±72.62	125.27±95.37	123.99±93.63	0.854[2]
csDMARD								
MTX	6 (25%)	42 (31.8%)	0.506[1]	4 (25%)	2 (25%)	42 (31.8%)	48 (30.8%)	0,801[1]
SSZ	4 (16.7%)	22 (16.7%)	1[1]	2 (12.5%)	2 (25%)	22 (16.7%)	26(16.7%)	0,741[1]
LEF	5 (20.8%)	14 (10.6%)	0.159[1]	2 (12.5%)	3 (37.5%)	14 (10.6%)	19 (12.2%)	0,078[1]
HCQ	3 (12.5%)	9 (6.8%)	0.337[1]	3(18.8%)	0	9 (6.8%)	12 (7.7%)	0,168[1]
b/tsDMARD								
ADA	2 (20%)	21 (30.4%)		2 (25%)	0	21 (30.4%)	23 (29.1%)	
ETN	2 (20%)	16 (23.2%)		2 (25%)	0	16 (23.2%)	18 (22.8%)	
GOL	1 (10%)	16 (23.2%)		1 (12.5%)	0	16 (23.2%)	17 (21.5%)	
IFX	1 (10%)	5 (7.2%)	0.387[1]	1 (12.5%)	0	5 (7.2%)	6 (7.6%)	0.002[1]
CTZ	1 (10%)	3 (4.3%)		1 (12.5%)	0	3 (4.3%)	4 (5.1%)	
RTX	1 (10%)	1 (1.4%)		0	1 (50%)	1 (1.4%)	2 (2.5%)	
SEC	0	4 (5.8%)		0	0	4 (5.8%)	4 (5.1%)	
TOC	1 (10%)	2 (2.9%)		0	1 (50%)	2 (2.9%)	3 (3.8%)	
TOF	1 (10%)	1 (1.4%)		1 (12.5%)	0	1 (1.4%)	2 (2.5%)	
DMARD groups								
csDMARD	14 (58.3%)	63 (47.7%)	0.633[1]	8 (50%)	6 (75%)	63 (47.7%)	77 (49.4%)	**0.544[1]**
b/tsDMARD	8 (33.3%)	55 (41.7%)		7 (43.8%)	1 (12.5%)	55 (41.7%)	63 (40.4%)	
combined	2 (8.3%)	14 (10.6%)		1 (6.2%)	1 (12.5%)	14 (10.6)	**16 (10.3%)**	

[1]Student's t-test; [2]ANOVA
SD: standard deviation, COVID-19: Coronavirus disease-2019, RA: Rheumatoid arthritis, AS: Ankylosing spondylitis, PsA: Psoriatic arthritis, DMARD: Disease modifying anti-rheumatic drugs, csDMARD: Conventional synthetic disease modifying anti-rheumatic drugs, b/tsDMARD: Biologic or targeted synthetic disease modifying anti-rheumatic drugs, MTX: Methotrexate, SSZ: Sulfasalasine, LEF: Leflunomide, HCQ: Hydroxychloroquine, ADA: Adalimumab; ETN: Etanercept, GOL: Golimumab, IFX: Infliximab, CTZ: Certolizumab pegol, RTX: Rituximab, SEC: Secukinumab, TOC: Tocilizumab, TOF: Tofacitinib

COVID-19 severity. We found that severe COVID-19 is more common in patients with CRD or with one or more comorbid diseases. We also found a higher rate of getting COVID-19 in those with moderate or high rheumatic disease activity. We showed that during the pandemic period, patients' compliance with their follow-up and treatment was low, and that rheumatic disease activity increased more frequently in those who made changes in their rheumatic disease treatment.

Two studies have been published from the COVID-19 Global Rheumatology Alliance (GRA) registry data on the factors affecting the risk of hospitalization and death from COVID-19 in those with rheumatic diseases (12,16). Among these, in the study evaluating the risk of hospitalization, advanced age, presence of comorbidities, and prednisone use (≥10 mg/day) were associated with a higher rate of hospitalization. Monotherapy with b/tsDMARD is associated with lower odds of hospitalization, largely due to the effect of anti-TNF treatments (12). In the study about COVID-19-related death, advanced age, male gender, specific comorbidities, and moderate/high disease activity were associated with higher risk (16). Similarly, we found a significant association between having a CRD or having more than one comorbid disease and COVID-19 severity. We did not find any difference between the patient groups using csDMARD, b/tsDMARD, and combined DMARD (cDMARD + b/tsDMARD) in terms of COVID-19-related outcomes. In a review of patients with autoimmune diseases, baseline glucocorticoid use and some specific drugs such as RTX and SSZ are associated with adverse COVID-19 outcomes, but no increased risk is observed for DMARD classes (13). In line with the COVID-19 GRA results reporting a protective effect with bDMARD use (mainly attributed to TNFis), a lower risk of COVID-19 related hospitalization is reported in patients with inflammatory bowel disease

Table 3. Demographic data, rheumatic diseases and treatments, PCR test & CT results, and COVID-19 treatments of patients with COVID-19

No	Age	Gender	Disease	DMARD	PCR	CT	COVID-19 treatment
1	53	F	AS	CTZ	Pos	No	Home, favipiravir
2	58	F	RA	LEF	Pos	No	Home, favipiravir
3	51	F	RA	MTX	Pos	Yes, typical	PLQ at home first, then favipiravir at hospital
4	47	F	RA	LEF	Pos	Yes, typical	Hospital, lopinavir-ritonavir and oseltamivir
5	66	F	RA	RTX	Pos	Yes, typical	Hospital, lopinavir-ritonavir, oseltamivir, azithromycin
6	66	M	RA	MTX	Neg	Yes, typical	Home, favipiravir
7	48	M	RA	SSZ	Pos	No	Home, HCQ and favipiravir
8	48	F	AS	IFX	Pos	No	Home, favipiravir
9	52	F	AS	SSZ	Pos	Yes, typical	Home, HCQ and favipiravir
10	60	F	RA	MTX	Pos	No	Home, favipiravir
11	61	F	RA	HCQ	Pos	No	Home, with increased HCQ dose
12	28	M	AS	ADA	Pos	No	Home, favipiravir
13	52	F	RA	HCQ	Pos	No	Home, favipiravir
14	63	F	RA	TOC+LEF	Pos	Yes, typical	Hospital, remdesivir and dexamethasone
15	27	F	RA	TOF+MTX	Pos	No	Home, favipiravir
16	54	F	RA	LEF	Pos	No	Home, favipiravir
17	46	F	AS	GOL	Pos	No	Home, favipiravir
18	37	F	AS	SSZ	Pos	Yes, typical	Hospital, HCQ, azithromycin, oseltamivir, favipiravir
19	40	M	AS	ADA	Pos	No	Home, favipiravir
20	35	F	RA	MTX+SSZ+HCQ	Pos	No	Home, favipiravir
21	38	F	AS	ETN	Pos	No	Home, favipiravir
22	52	M	PsA	MTX	Pos	No	Home, HCQ and favipiravir
23	69	F	RA	LEF	Pos	Yes, typical	ICU, favipiravir, methylprednisolone, high dose vitamin C, mechanical ventilation
24	37	M	AS	ETN	Pos	No	Home, favipiravir

F: Female, M: Male, COVID-19: Coronavirus disease-2019, RA: Rheumatoid arthritis, AS: Ankylosing spondylitis, PsA: Psoriatic arthritis, DMARD: Disease modifying anti-rheumatic drugs, MTX: Methotrexate, SSZ: Sulfasalasine, LEF: Leflunomide, HCQ: Hydroxychloroquine, ADA: Adalimumab, ETN: Etanercept, GOL: Golimumab, IFX: Infliximab, CTZ: Certolizumab pegol, RTX: Rituximab, TOC: Tocilizumab, TOF: Tofacitinib, PCR: Polymerase chain reaction, Pos: Positive, Neg: Negative, CT: Computed tomography, ICU: Intensive care unit

using TNFi monotherapy (17) and in patients with psoriasis using bDMARD (compared to non-bDMARD) (18). In addition to the risk factors mentioned above, the delayed diagnosis of COVID-19 was found to be a risk factor for hospitalization (19). Although there was no difference in COVID-19-related outcomes between DMARD classes in our study, the relationship between leflunomide use and severe COVID-19 findings was remarkable, although not statistically significant. In a study evaluating the risk of COVID-19 in patients using DMARD, a positive association was found between the use of leflunomide and the risk of COVID-19 infection (20). On the other hand, another study highlights the potential antiviral effects of leflunomide, noting that it provides faster recovery and reduced viral clearance time in patients with COVID-19 (21).

Another remarkable finding is the opposite relationship between smoking and COVID-19 in our study. 16.7% of the patients who got COVID-19 and 42.4% of those who did not were active smokers. A study supporting this finding found lower probability of testing positive for Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in active smokers than in non-smokers (22). In the study, this was explained by nicotine down-regulation of ACE-2 receptors, which SARS-CoV-2 uses to enter the cell, but the authors emphasized that this should not be interpreted as a protective effect of smoking against COVID-19 (22). In

addition, another study reported that smoking is associated with negative progression and adverse outcomes of COVID-19 (23).

A significant portion of the patients in this study thought that they were in the risk group for COVID-19 because of their rheumatic diseases and the DMARD they used. A similar finding is seen in a study from Australia, where 41% and 55.7% of patients expressed concern about the increased risk of getting COVID-19 due to their rheumatological diseases and medications, respectively. In the same study, in terms of severe COVID-19 results, 52.3% of the patients had a perception of increased risk due to rheumatological diseases and 76.1% due to their medications (2). As a predictable consequence of this situation, patients' compliance with follow-up and treatment decreased. In a study of individuals with RA in the United States, 30% of patients reported a change in treatment, and the proportion who canceled or postponed their appointments (varying in different DMARD groups) was between 28% and 35% (24). In this study, 25% of the patients attended their appointments regularly, and 67% continued their treatment as before. Similar results were observed in other studies in our country. In a study evaluating 330 patients with inflammatory rheumatic diseases in Ankara, it was observed that 27.2% of the patients continued their follow-up regularly and 11.9% changed their treatment without a doctor's advice. In a web-based survey study from İstanbul, these rates for adherence were as follows; 14.4% for follow-up and 77% for treatment. In the latter, similar to our study, there was a significant difference between the RA (81.3%) and SpA (46.3%) patient groups who continued the treatment as before. Similarly, in the study of Kalyoncu et al. (25) evaluating the preferences of patients using bDMARD for the treatment of inflammatory arthritis, the proportion of patients who discontinued bDMARD therapy was significantly higher in the SpA group (20.5%) than in the RA group (13.8%). They also showed lower disease activity in SpA patients who continued bDMARD therapy, in line with the higher incidence of increased disease activity in patients who discontinued DMARD therapy in our study. In our study, the rates of continuing routine treatment were 83.1% in the RA group and 55.3% in the SpA group, which was statistically significant. In addition, the results of a survey study in Spain are similar to our results both in terms of treatment adherence, of which 79.7% of patients continued their treatment as before and in terms of the relationship between spacing-stopping treatment and worsening disease activity (26).

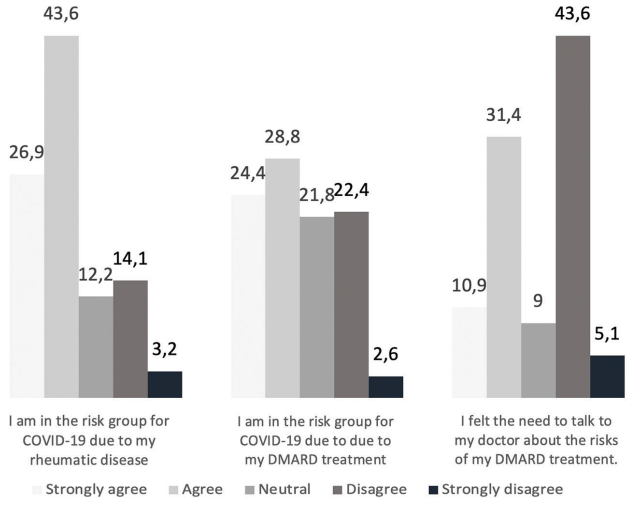

Figure 1. COVID-19 risk perceptions
COVID-19: Coronavirus disease-2019

Table 4. Rheumatic disease activities of the patients before and during the pandemic

Disease activity	After (During pandemic)				P[1]
	<0.001				
Before	**R**	**L**	**M**	**H**	
R	40	12	13	2	
L	1	41	1	27	
M	3	7	3	0	
H	0	1	1	4	

[1]McNemar's test
R: Remission, L: Low, M: Moderate, H: High

Table 5. COVID-19 status and changes in rheumatic disease activity

	COVID-19 situation							
	Getting COVID-19			COVID-19 severity				
	Yes (n=24)	No (n=132)	p	Mild (n=16)	Severe (n=8)	Did not get (n=132)	Total (n=156)	p
Disease activity								
R/L	12 (50%)	93 (70.5%)	**0.049**[1]	9 (56.2%)	3 (37.5%)	93 (70.5%)	105 (67.3%)	0.095[1]
M/H	12 (50%)	39 (29.5%)		7 (43.8%)	5 (62.5%)	39 (29.5%)	51 (32.7%)	

[1]Chi-square test
COVID-19: Coronavirus disease-2019, R: remission, L: Low, M: Moderate, H: High

The most important limitation of our study is the absence of a control group consisting of patients with rheumatic disease who did not use DMARD. Therefore, COVID-19-related outcomes in patients with rheumatic diseases and using DMARD for treatment could not be compared with patients who did not use DMARD. Another limitation is the small number of patients compared with similar studies in the literature. Patients' hesitance to come to the hospital may have caused this situation.

CONCLUSION

There is no difference in COVID-19-related outcomes between DMARD classes in patients with rheumatic diseases. Having a CRD or one or more comorbid diseases may increase the risk of severe COVID-19 manifestations. Patients with moderate or high rheumatic disease activity may get COVID-19 more frequently. Patients' perception of risk for COVID-19 has reduced compliance with follow-up and treatment, making it difficult to maintain remission or low disease activity.

ETHICS

Ethics Committee Approval: We obtained the Clinical Research Ethics Committee approval from University of Health Sciences Türkiye, İstanbul Fatih Sultan Mehmet Training and Research Hospital (no: FSM EAH-KAEK 2020/95, date: 09.07.2020) for this study.

Informed Consent: Written informed consent was obtained from all participants.

Authorship Contributions

Surgical and Medical Practices: K.S., F.Ü.Ö., İ.A., Concept: K.S., F.Ü.Ö., İ.A., P.A., Design: K.S., F.Ü.Ö., İ.A., P.A., Data Collection or Processing: K.S., Analysis or Interpretation: K.S., F.Ü.Ö., İ.A., Literature Search: K.S., Writing: K.S., F.Ü.Ö., İ.A., P.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial support.

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