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Coronavirus Pandemic

How has the COVID-19 pandemic affected our rheumatology patients using biological/targeted DMARDs?

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Abstract

Introduction: We aimed to investigate the effects of the coronavirus disease 2019 (COVID-19) pandemic on the course and treatment of patients with inflammatory rheumatic musculoskeletal disease (iRMD) using biologic or targeted synthetic disease modifying and rheumatic drugs (b/tsDMARDs).

Methodology: The study was carried out in two stages: in the first stage we investigated the delay of b/tsDMARD treatment in the first 3 months of the pandemic; in the second stage, we investigated all patients who decided to continue treatment after interruption in the 12-month period.

Results: A total of 521 patients were included in the study. The iRMD diagnosis was listed as spondyloarthritis (SpA) (54.3%), rheumatoid arthritis (RA) (25.7%), psoriatic arthritis (PsA) (8.4%), vasculitis (6.1%), and others (5.4%). Concurrent use of hydroxychloroquine (hazard ratio [HR] = 1.49), iv bDMARD use (HR = 1.34), and a history of discontinuation of drug in the first 3 months of the pandemic (HR = 1.19) were determined as factors that reduced 12-month drug retention rates. The use of glucocorticoid (HR = 3.81) and having a diagnosis of interstitial lung disease/chronic obstructive lung disease (HR = 4.96) were found to increase the risk of being infected by SARS coronavirus 2 (SARS-CoV-2).

Conclusions: It was shown that approximately 1/5 of iRMD patients using b/tsDMARDs delayed their treatment due to the fear of COVID-19 in the first three months of the pandemic process. However, with good communication with the patients, b/tsDMARD treatment was restarted and the 12-month drug retention status was quite high.

Key words: COVID-19; SARS-COV-2; pandemic; rheumatology; biologic therapy; b/tsDMARD.

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 [1], and has caused adverse effects in our country as well as all over the world. This has led to doubts as to whether the treatment of patients using immunosuppressive drugs should be continued [2]. While the coronavirus disease 2 (COVID-19) is asymptomatic, mild, or moderate in severity in the vast majority of patients (80%), it causes severe pneumonia and hypoxemia in approximately 14% and severe clinical manifestations such as severe respiratory failure, septic shock and multiorgan failure in approximately 6% of patients [3].

Data show that male gender, advanced age, smoking, and comorbidities are associated with poor outcome of COVID-19. The thought that the risk of being infected with the SARS-CoV-2 virus and the possibility of a poor clinical course may be high in patients using biological or targeted disease-modifying anti rheumatic drugs (b/ts DMARDs) for inflammatory rheumatic musculoskeletal diseases (iRMD) has led to serious concerns, especially in the early stages of the pandemic [4]. However, it is well known that the active disease state that may occur as a result of discontinuing the drugs also increases the susceptibility to infection.

In the current study, we aimed to investigate the frequency of interruption/stopping and re-starting the treatment during the pandemic period for patients diagnosed with iRMD and using b/ts DMARDs who followed up in our clinic, to investigate the results of these conditions, and to evaluate the clinical features and outcomes of patients with COVID-19.

Methodology

Patients

Patients with a diagnosis of iRMD and using b/tsDMARD who were followed up in the Rheumatology Clinic of Dokuz Eyul University Faculty of Medicine during the 12-month period (March 11, 2020 – March 11, 2021) from the onset of the pandemic

were included in this study. Patients were interviewed face-to-face or via telephone/e-mail by rheumatology fellows (SG, TI, AK) and clinical nurses (BB, BD). Since the patients were regularly called, at least every 3 months, it was primarily aimed to reach the patients who applied to the outpatient clinic in the 3 months before the pandemic.

The study was carried out in two stages. In the first stage, the situation of delaying b/tsDMARD treatment in the first three months of the pandemic (11 March - 11 June 2020) due to the fear of getting infected with COVID-19 was investigated, while in the second stage, we investigated whether all patients, whose decision to continue treatment was clarified as a result of physician-patient interviews at the end of three months, continued their drug in the first 12 months of the pandemic (March 11, 2020 - March 11, 2021).

Apart from the concern of getting infected with COVID-19, other factors affecting drug retention, activation of rheumatic disease upon drug retention, frequency of infection with COVID-19 during this period, and course of infection were evaluated using standardized questionnaires. Gender, age, time elapsed after diagnosis (disease duration), comorbidities, and smoking habits of the patients were recorded. The pre-pandemic planned treatments of the patients were evaluated through their last visit registered in the TURKBIO database [5]. During the study period interviews, the drugs currently used by the patients [NSAID (nonsteroidal anti-inflammatory drug), glucocorticoid (GC), conventional DMARD, conventional synthetic DMARD) and b/ts DMARD] and their doses were recorded.

Patients who did not come for regular check-ups, who could not control the disease before the declaration of the pandemic, whose regular drug follow-ups could not be reached, whose data on COVID-19 could not be accessed and who did not want to participate in the study were not included. Written and verbal consents were obtained from all patients participating in the study.

Disease activity measurements

During the interviews with the patients, whether the rheumatic disease was active or not was decided according to the global evaluations of the patients and physicians. Disease activation was evaluated according to expert opinion after detailed examination and laboratory examination of all patients. An increase in the dose of GCs was also evaluated in favor of activation of the disease. In addition, the old and new findings of the patients registered in the TURKBIO (Turkey) database and use of biological therapy were compared. Biological treatment responses of the patients were evaluated according to primary and secondary non-response status in the light of current guidelines. Drug unresponsiveness of patients diagnosed with Behçet's disease, sarcoidosis and familial Mediterranean fever (FMF) was evaluated with the expert opinion of the patients. Patients who underwent treatment change due to primary unresponsiveness during the study were not included.

In these interviews, the disease statuses and the risks involved were evaluated and together with patients the future treatment course was decided. Risk assessments were made about whether the patients should come to the hospital for control.

COVID-19 data

All patients were questioned at regular intervals (monthly) regarding the development of COVID-19 during the study period. Patients with infection were evaluated in terms of associated symptoms, diagnosis, severity of disease, hospitalization status, intensive care needs, and clinical outcomes. Treatments used for COVID-19 and disease severities of patients were defined in accordance with the current "WHO and Turkish Ministry of Health COVID-19 Diagnosis and Treatment Guidelines" [1]. The 30-day mortality risk of the patients at the time of diagnosis of COVID-19 was evaluated with the Veterans Health Administration COVID-19 Index (VACO) (%) [6]. During this period, patients diagnosed with COVID-19 were followed up until recovery or death. All data of the patients were updated on the last date of the study (March 11, 2021), and the study ended.

Ethical statement

This study was approved by the Dokuz Eylul University Ethics Commission (Approval Number: 2019 Issue No: 09-24) and was conducted in accordance with the Declaration of Helsinki. In addition, a "Letter of Approval from the Turkish Ministry of Health COVID-19 Studies" was received for the study. Written informed consent was obtained from all patients included in our study.

Statistical analysis

The SPSS 25.0 (IBM Corporation, Armonk, New York, United States) program were used for the analysis of the variables. The conformity of the data to the normal distribution was evaluated with the Shapiro-Wilk Francia test and the homogeneity of variance was evaluated with the Levene test. The independent-

samples t test was used together with the bootstrap results, while the Mann-Whitney U test was used with the Monte Carlo simulation technique in the comparison of two independent groups according to quantitative data. In the comparison of categorical variables, the Pearson Chi-square, linear-by-linear association and Fisher-Freeman-Holton tests were used with the Monte Carlo simulation technique, while the Fisher exact test was performed using the exact results and the column ratios were compared with each other and expressed according to the Benjamini-Hochberg corrected *p* value results. While the quantitative variables were expressed as mean ± SD (standard deviation) and median (minimum-maximum), the categorical variables were shown as n (%) in the tables. A logistic multivariate regression model with stepwise backward Wald elimination (disease exacerbation over 12 months and to be infected by SARS-CoV-2) was used to examine associations with outcome. In the case of covariates in the models, the *p* value was determined as 0.15 in the univariate analysis, the probability of gradual entry was 0.05 and the probability of removal

Table 1. Demographic data of patients who regularly used and interrupted treatment in the first 3 months.

Characteristics	**Total (n = 521)**	**b/tsDMARD Continue (n = 424)**	**b/tsDMARD Interruption (n = 97)**	***p***
	Median (Min./Max.)	**Median (Min./Max.)**	**Median (Min./Max.)**	
Age (years)	48 (18/86)	47 (18/82)	52 (21/81)	**0.008***
Disease duration (months)	134,4 (22/519)	130 (22/490)	142 (22/519)	0.41
b/ts DMARD duration (months)	40 (12/192)	40 (12/192)	40 (12/156)	0.176
	n (%)	**n (%)**	**n (%)**	
Gender				
Female	278 (53.4)	225 (53.1)	53 (54.6)	0.826
Male	243 (46.6)	199 (46.9)	44 (45.4)	
Age group (years)				
< 30	52 (10)	44 (10.4)	8 (8.2)	0.58
30-49	230 (44.1)	**194 (45.8)**	36 (37.1)	0.138
50-65	183 (35.1)	148 (34.9)	35 (36.1)	0.907
> 65	56 (10.7)	38 (9)	**18 (18.6)**	**0.007***
Disease activation (during pandemic)	92 (17.7)	14 (3.3)	78 (80.4)	**< 0.001****
COVID-19 during follow-up	34 (6.5)	24 (5.7)	10 (10.3)	0.113
Most common rheumatic diseases				
AxSpa or other SpA Types	283 (54.3)	232 (54.7)	51 (52.6)	0.737
Rheumatoid artrhritis	134 (25.7)	100 (23.6)	34 (35.1)	**0.015***
Psoriatic Arthritis	44 (8.4)	40 9.4)	4 (4.1)	0.109
Vasculitis	32 (6.1)	27 (6.4)	5 (5.2)	0.817
Others	28 (5.4)	25 (5.9)	3 (3.1)	0.338
Rheumatic medication				
bDMARD only	334 (64.1)	273 (64.4)	61 (62.9)	0.528
bDMARD + csDMARD	158 (30.3)	126 (29.7)	32 (33)	
tsDMARD only	6 (1.2)	5 (1.2)	1 (1)	
tsDMARD + csDMARD	23 (4.4)	20 (4.7)	3 (3.1)	
HCQ use	29 (5.6)	14 (3.3)	15 (15.5)	**0.001***
GC use	100 (19.2)	78 (18.4)	22 (22.7)	0.394
b/tsDMARD stopped permanently	29 (5.6)	9 (2.1)	20 (20.6)	**< 0.001^{ff*}**
Patients did not want to start b/tsDMARD again	24 (4.6)	4 (0.9)	20 (20.6)	**< 0.001^{ff*}**
Deceased	5 (1)	3 (0.7)	2 (2.1)	0.415
b/tsDMARD retention (Total)	474 (91)	406 (95.8)	68 (70.1)	**< 0.001****
Comorbidities				
HT	151 (29)	122 (28.8)	29 (29.9)	0.904
DM	71 (13.6)	57 (13.4)	14 (14.4)	0.875
COPD+ILD	18 (3.5)	12 (2.8)	6 (6.2)	0.126
CVD	39 (7.5)	32 (7.5)	7 (7.2)	0.911
CKD/ESRD	16 (3.1)	13 (3.1)	3 (3.1)	0.989
Smoking (ever)	316 (60.7)	265 (62.5)	51 (52.6)	0.071

Independent Samples t test (Bootstrap), Pearson Chi-square test (Monte Carlo), Fisher Freeman Halton test (Monte Carlo), linear-by-linear association test(Monte Carlo, exact). Min: minimum; Max= maximum; n: number; b/tsDMARD: biological or targeted synthetic DMARD; DMARD: disease modifying anti-rheumatic drugs; AxSpA: axial spondyloarthritis; HT: hypertension; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; ILD: ınterstitial lung disease; CVD: cardiovascular disease; CKD: chronic kidney disease; ESRD: end stage renal disease; HCQ: hydroxychloroquine; GC: glucocorticoid; *: $p < 0.05$; **: $p < 0.001$.

was 0.10. The variables were analyzed at 95% confidence level and $p < 0.05$ was considered significant.

Results

Patients

The number of patients admitted to the hospital due to the pandemic has decreased significantly since March 16, 2020. Therefore 75% of the interviews were made via telephone/e-mail. Face-to-face interviews were conducted with patients admitted to the hospital. A total of 521 (278 women) patients with a diagnosis of iRMD who were registered and contacted in the first 3 months of the pandemic and whose disease was inactive or in remission with b/ts DMARD at the time the pandemic started were included in the study. The median age of the patients was 48 (range 18 to 86) years. The median disease duration of follow-up was 134.4 (22 to 519) months, and the duration of b/tsDMARD use was 40 (12 to 192) months. The most common diagnosis of rheumatic disease was spondyloarthritis (SpA) in 283 (54.3%) patients, while 134 (25.7%) patients were diagnosed with rheumatoid arthritis (RA), 44 (8.4%) patients with psoriatic arthritis (PsA), 32 (6.1%) patients with vasculitis (Behçet's Disease, granulomatosis polianjiitis, Takayasu's arteritis) and 28 (5.4%) patients with other diseases (adults onset Still's disease, sarcoidosis, uveitis, FMF etc.) (Table 1).

Comorbidities

Of the patients, 46% had at least one comorbidity and 25.1% had two or more comorbidities. Although the patients were most frequently diagnosed with hypertension (HT) (n = 151, 29%); diabetes mellitus (DM) (n = 71, 13.6%), interstitial lung disease/chronic obstructive lung disease (ILD/COPD) (n = 18, 9.2%), cardiovascular disease (CVD) (n = 39, 7.5%) and chronic kidney disease/end stage renal disease (CKD/ESRD) (n = 16, 3.1%) were also detected in decreasing order of frequency. The rate of smoking (ever) among the patients was 60.7% (Table 1).

Treatments

When the patients were evaluated according to the b/tsDMARD treatments they were using, it was determined that 334 (64.1%) patients received the bDMARD treatment, 158 (30.3%) patients used the bDMARD + csDMARD combination, 23 (4.4%) patients used the tsDMARD + csDMARD combination, and 6 (1.2%) patients used only tsDMARD. The most commonly used bDMARD was Adalimumab (n = 117, 225%), followed by infliximab (n = 103, 19.8%), etanercept (n = 101, 19.4%), certolizumab (n = 57, 10.9%), and golimumab (n = 25, 4.8%) (data not shown).

A total of 29 (5.6%) patients received the tsDMARD tofacitinib treatment. While 21 (4%) patients were received the IL-6 inhibitor (tocilizumab), 23 (4.4%) patients received the IL17A inhibitor (secukinumab) and 14 (2.7%) patients received the CTLA4 inhibitor (abatacept). It was observed that 15 (2.9%) patients used rituximab (RTX) treatment. Of the patients, 100 (19.3%) used GC and 29 (5.6%) used hydroxychloroquine (HCQ) concurrently. When b/ts DMARD treatments were evaluated according to the treatment administration routes, 137 (26.3%) patients were using [infliximab, tocilizumab (iv.) or abatacept (iv.)] intravenously, 355 (68.1%) patients were using subcutaneous (SC) route and 29 patients were using oral tsDMARD (Table 1).

Disease activity

During the 12-month follow-up, a rheumatic disease was activated in 92 (17.7%) of 521 patients. Disease activation occurred in 78 (79.4%) of 97 patients in the group who stopped taking their drugs in the first 3 months of the pandemic, and in 14 (3.3%) of the patients who used their drugs regularly in the first 3 months ($p < 0.001$) (Table 1). As a result, 471 of 516 patients who decided to use regular treatment at the end

Table 2. Factors affecting drug retention rates in all patients.

	HR	95% CI for Hazard Ratio		*p*
		Lower	Upper	
Gender, Male	0.196	0.077	0.198	**< 0.001**
Comorbidity ≥ 2	0.409	0.174	0.614	**0.001**
Rheumatoid Arthritis	0.326	0.063	0.26	**< 0.001**
HCQ use	1.494	1.395	14.39	**0.012**
b/ts DMARD use in Hospital (intravenous bDMARD)	1.335	0.132	0.487	**< 0.001**
Drug interruption first three months of pandemic	1.192	1.64	5.448	**< 0.001**

Multiple Logistic Regression (Method Enter) was used for defining factors affecting the drug retention rates. Variables with $p < 0.01$ in the model were included in the multiple logistic regression analysis. HR: hazard ratio; 95% CI: 95% confidence interval; HCQ: hydroxychloroquine; DMARD: Disease modifying anti rheumatic drgus; b/tsDMARD: biological or targeted synthetic DMARD.

Table 3. Comparison of demographic and clinical characteristics of patients with COVID-19.

Demographics	COVID-19 (-) (n: 487)	COVID-19 (+) (n: 34)	*p*
	Median (Min./Max.)	Median (Min./Max.)	
Age	48 (18-86)	48 (18-82)	0.615
Disease Duration	130 (22-478)	144 (48-519)	0.573
b/ts DMARD Duration	45 (12-192)	26 (14-170)	0.253
GC dose, mg	4 (1-16)	4 (2-16)	0.863
VACO Index	–	0.4 (0.3 - 29.4)	–
	n (%)	n (%)	
Gender, Female	259	19	0.909
Most common rheumatic diseases			**< 0.001****
AxSpa or other SpA Types	**270 (55.4)**	13 (38.2)	
Rheumatoid artrhritis	122 (25.1)	**12 (35.3)**	
Psoriatic Arthritis	29 (6.0)	3 (8.8)	
Vasculitis	23 (4.7)	**5 (14.7)**	
Others	**43 (8.8)**	1 (2.9)	
COVID-19 diagnosis and outcome			
PCR	–	21 (61.8)	–
PCR+Thorax CT	–	13 (38.2)	–
Hospitalization	–	11 (32.3)	–
Severe COVID-19	–	8 (23.5)	–
Mortality	–	5 (14.7)	–
Active disease (anytime during the pandemic)	82 (16.4)	9 (26.5)	0.246
Comorbidity ≥ 2	104 (21.8)	27 (60.0)	0.936
Smoking (ever)	291 (61.1)	25 (55.6)	0.373
HT	134 (28.2)	17 (37.8)	0.070
DM	63 (13.2)	8 (17.8)	0.688
ILD and/or COPD	14 (2.9)	**4 (8.9)**	**0.002***
CAD	35 (7.4)	4 (8.9)	0.321
b/tsDMARD combination with cDMARD			**0.028***
bDMARD only	319 (65.5)	15 (44.1)	
bDMARD + csDMARD	141 (28.9)	**17 (52.9)**	
tsDMARD only	5 (1.0)	1 (2.9)	
tsDMARD + csDMARD	22 (4.5)	1 (2.9)	
	n (%)	n (%)	
b/tsDMARD type			**0.049***
TNFi	**382 (78.4)**	15 (44.1)	0.243
Tocilizumab	19 (3.9)	2 (5.9)	0.684
Abatacept	13 (2.7)	1 (2.9)	0.886
RTX	9 (1.8)	**6 (17.6)**	**0.001***
Tofacitinib	27 (5.5)	2 (5.9)	0.884
GC	83 (17.0)	**17 (50.1)**	**0.001***
b/tsDMARD continue	448 (92.0)	28 (82.5)	0.120

Tests used for group comparisons: Independent Samples t Test (Bootstrap); Pearson Chi-Square Test (Monte Carlo); Fisher freeman Halton Test (Monte Carlo); Linear-by-Linear Association Test (Monte Carlo, Exact). SD: standard deviation; Min: minimum; Max: maximum; n: number; b/tsDMARD: biological or targeted synthetic DMARD; DMARD: disease modifying anti-rheumatic drugs; AxSpA: axial spondyloarthritis; HT: hypertension; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; ILD: ınterstitial lung disease; CVD: cardiovascular disease; CKD: chronic kidney disease; ESRD: end stage renal disease; HCQ: hydroxychloroquine; GC: glucocorticoid; PCR: polymerase chain reaction; CT: computed tomography; TNFi: tumor necrosis factor inhibitor; RTX: rituximab; *: $p < 0.05$; **: $p < 0.001$.

Table 4. Multiple logistic regression analysis evaluating the risk of infection with SARS-CoV-2.

	HR	95% CI for Hazard Ratio		*p*
		Lower	Upper	
Hypertension	0.645	0.303	1.377	0.257
GC use	3.813	1.497	9.71	**0.005***
Combination (Reference: tsDMARD+csDMARD)				
bDMARD only	1.69	0.169	16.927	0.655
bDMARD + csDMARD	3.215	0.357	28.931	0.297
tsDMARD only	2.516	0.102	61.747	0.572
COPD/ILD	4.976	1.386	17.862	**0.014***

Multiple Logistic Regression (Method Enter) model was used for evaluating the risk for COVID-19. Variables with $p < 0.01$ in the model were included in the multiple logistic regression analysis. HR: hazard ratio; CI: confidence interval; COPD: chronic obstructive pulmonary disease; ILD: ınterstitial lung disease; b/tsDMARD: biological or targeted synthetic DMARD; DMARD: disease modifying anti-rheumatic drugs; GC: glucocorticoid; *: $p < 0.05$; **: $p < 0.001$.

The incidence of interstitial lung disease was higher in patients who had COVID-19 (8.9% vs 2.9%) (p = 0.002). The frequency of bDMARD + csDMARD combination was found to be higher in patients who had COVID-19 compared to patients who did not (52.9% vs 28.9%) (p = 0.028). The frequency of using RTX in patients who had COVID-19 was considerably higher than those who did not (17.6% vs 1.8%) (p < 0.001). The rate of using TNFi in patients who had COVID-19 was found to be lower than those who did not (44.1% vs 78.4%) (p = 0.016) (Table 3).

In the multiple logistic regression analysis, it was determined that the use of corticosteroid (CS) (HR: 3.81, 95% CI, 1.49 – 9.71, p = 0.005) and having a diagnosis of ILD and/or COPD (HR: 4.976, 95% CI, 1.39-17.86, p = 0.014) increased the risk of getting infected with COVID-19. There was no significant relationship between age, gender, intravenous bDMARD use, smoking, b/tsDMARD type, and b/tsDMARD + csDMARD combination (compared to bDMARD alone) and the development of COVID-19 (Table 4).

Discussion

In this study, it was observed that 97 (18.6%) of 521 patients with iRMD who used b/tsDMARD interrupted their drug due the fear of being infected with SARS-CoV-2 in the first 3 months of the pandemic process. Interruption of treatment was more common in older patients, patients with RA, and those with a shorter duration of b/tsDMARD use. After the interviews in the first three months, 92 patients decided to use their treatment regularly. At the end of 12 months, the frequency of continuing the drug was quite high (92.3%). It was observed that the frequency of continuing the drug at 12 months was higher in those who used their treatment regularly from the beginning, compared to those who interrupted the treatment in the first 3 months.

Patients with iRMD are generally thought to be more prone to bacterial and certain viral infections such as herpes zoster virus [7,8]. While patients using b/tsDMARD therapy have a higher risk of infection compared to the normal population, this situation had become a more difficult problem to solve during the pandemic period [9]. In a multi-center study by George *et al*. [10], including 1517 participants (arthritis power patient-powered research network and creaky joints patient community completed surveys), it was determined that the concern of COVID-19 was similar across the country in the people in the iRMD database study, but higher in patients using b/tsDMARD (p < 0.001) and it was observed that 14.9% of the patients interrupted b/tsDMARD treatment even though they did not have any infections (925 RA, 299 PsA, 185 ankylosing spondylitis [AS], 108 systemic lupus eritematosus [SLE]). In this study, people who interrupted/disrupted b/tsDMARD treatment avoided hospital admissions (OR: 1.46, 95% CI: 1.04-2.04) or could not reach tele-health services because of their lower socioeconomic statuses (OR: 2.26, 95% CI: 1.25-4.08).

It is known that the presence of active disease is an important factor that increases the susceptibility to infections, in addition to the use of immunosuppressive drugs in iRMD patients. In a US registry study involving more than 16,000 patients, it was shown that each 0.6 point increase in the RA disease activity score (DAS) resulted in a 25% increase in the risk of infection requiring hospitalization and a 4% increase in outpatient infections [11]. Therefore, the risk of activation of the rheumatic disease due to the drugs being discontinued is not a desirable situation. In the present study, it was noted that patients who discontinued their biologic therapy had significant increases in disease activity (79.4% vs. 3.3%) compared to those who did not. Consequently, there were more hospital admissions, increased use of NSAIDs and CS (data not shown). This situation caused patients trying to reduce the risk of infection to enter an important vicious circle. However, in this study, a number of patients who could have a significant relationship with active disease in terms of the development and severity of COVID-19 could not be reached.

From the beginning of the pandemic, the Turkish Rheumatology Association provided detailed information including the opinions of experts and associations in line with the world's leading rheumatology associations and organizations: European Alliance of Associations for Rheumatology (EULAR), British Society of Rheumatology (BSR) and American College of Rheumatology (ACR), to respond to the questions of rheumatology patients and rheumatologists about the treatment [12,13]. They tried to continue the b/tsDMARD treatment of the patients and to use the lowest possible dose of CS or to discontinue the drug. In addition, SC was used in treatments with both forms (intravenous and SC) such as tocilizumab and abatacept in eligible patients. Switch recommendations were also made. During the treatment of 9 patients (7 tocilizumab and 2 abatacept) followed up in our clinic, the intravenous form was switched to the SC form. In our clinic, the doctors and nurses who reached out to patients receiving biologic therapy, tried

uninterruptedly to ensure that patients continued their current b/tsDMARD treatments in an optimal way. Thanks to these important dynamic changes, it was observed that the overall b/tsDMARD drug retention rate was significantly higher (92.3%) in the 12-month follow-up of the patients.

The incidence of COVID-19 was 6.5% among the 521 patients included in the study and using b/tsDMARD therapy, which was above the overall prevalence when compared to the current data. However, this value is only in patients who came to our outpatient clinic in the first 3 months of the pandemic or were contacted by phone/e-mail because they could not come, and whose disease was inactive under b/tsDMARD. Patients who were active before the pandemic or who discontinued their drug due to another infection or reason were not included in the study. In addition, the frequency may have been found to be higher than it was due to the possibility of detecting patients hospitalized in our hospital because of COVID-19 more easily. In Italy, one of the countries that was most severely affected by COVID-19 infection, COVID-19 was reported with a high frequency (117 or 8% of 1525 rheumatology patients) as we found in our study [14]. Similarly, bias may be present in this study as well. For the same reason, the hospitalization rate in COVID-19 patients (32.4%) was also found to be higher than was generally reported in this study. In addition to easier access to these patients, the difference in the adequacy of health services and hospitalization indications between countries may have affected this result. The fact that high hospitalization rates are not in line with the severe incidence of COVID-19 (15.9%) supports this idea.

The COVID-19 Global Rheumatology Association (GRA), an important case reporting record for rheumatologists early in the pandemic process, showed data from 600 patients and reported that most immunosuppressive drugs, including b/tsDMARD agents, were not associated with a significantly increased risk for hospitalization [15]. Conversely, in a study by Pablos *et al*. [16], conducted on a total of 456 hospitalized patients with a diagnosis of COVID-19 (228 with a diagnosis of iRMD, 23.2% using b/tsDMARDs), patients with a diagnosis of rheumatic disease were reported to have a 1.32-fold higher hospitalization rate compared to the reference population (0.58% versus 0.76%). However, in this study, it was thought that rheumatic patients using b/tsDMARDs were older and this could lead to an increase in the hospitalization rate. In the current study, there was no difference between the frequency of COVID-19 and the frequency of hospitalization in patients who continued or stopped using b/tsDMARD.

Subsequent data from the Global Rheumatology Alliance (GRA) trial [15] showed that use of prednisolone over 10 mg/day and steroid use at any dose in the SECURE-Inflammatory Bowel Disease registry [17] were associated with a higher risk of hospitalization and serious outcomes. However, a significant risk in terms of COVID-19-related clinical outcomes of immune modulators such as methotrexate, leflunomide, azathioprine, TNF-α inhibitor (TNFi) and Janus kinase inhibitor has not yet been reported [18,19]. Kristin *et al.* [20] determined that, similar to previous studies, csDMARD and b/tsDMARD treatments were not associated with poor COVID-19-related clinical outcomes. In this study, it was stated that the use of CS would pose a significant risk for the development of severe COVID-19. Although the use of CS appeared to increase the incidence of getting infected with COVID-19 in the current study, its impact on the development of severe COVID-19 could not be clearly demonstrated. However, it was interpreted that the very low daily GC doses used in our patients throughout the study (mean dose = 2 mg/day) may have affected this result. In line with our previous knowledge, the general view emerging in the recently updated literature is to not change the treatment used by patients unless COVID-19 symptoms occur [21,22].

In our study, additional CS was used (mean CS dose: 8 mg/day) in 3 of the 5 (14.7%) patients who died in the study group. The fact that two of the patients were due to RA-ILD and that all patients who died had at least one comorbidity may have contributed to the fatal outcome. These findings reinforce the reservations about the use of RTX and medium-high-dose CS in patients with iRMD and comorbidities in the ongoing COVID-19 pandemic. Obviously, the detection of COVID-19 in 6 of 15 patients who received RTX treatment in the study and the death of 2 patients, and the fact that CD20 inhibition creates a basis that will contribute to the easy development and poor outcome of the infection is remarkable. Although the use of RTX could not show an increase in risk for the development of COVID-19 in the logistic regression analysis, it was observed that having a diagnosis of ILD caused a significant increase in the risk (OR: 4.976, 95%, CI: 1.386-17.862; $p = 0.014$).

A French iRMD COVID-19 cohort, identified advanced age, male gender, obesity, and hypertension to be associated with severe COVID-19, as already defined in the general population [23]. In the aforementioned study, it was stated that the use of CS

creates an increased risk of severe COVID-19, and it was thought that they will have similar mortality rates when compared with the normal population in terms of age and comorbidities. However, it was emphasized that the risk of severe COVID-19 in patients with ILD or using RTX should be carefully evaluated [23]. In addition to the relatively small number of remarkable case reports, a recent GRA report concluded that RTX treatment causes an increased risk of COVID-19-related poor outcome [24]. B cell inhibition can potentially compromise antiviral immunity, including the development of SARS-CoV-2 antibodies.

Most studies conducted during the pandemic period demonstrated that older age and comorbidities, more than the diagnosis of iRMD and the immunosuppressive therapies used, increase the risk of infection with COVID-19; more serious outcome, and therefore hospitalization and death in the ICU [14,20,25–27]. At least 2 comorbidities were present in 25.1% of patients in the current study. In the study, it was observed that the presence of DM and 2 or more comorbidities increased the risk of COVID-19.

The current study has some inevitable limitations. There are more than thousand b/ts DMARD patients who are registered in the rheumatology clinic and come to regular follow-ups. During the pandemic, the patients' preferences for face-to-face interviews were changed to enroll in the TURKBIO cohort, and patients were allowed to continue their b/tsDMARD treatments unless otherwise stated. In addition, exacerbation status of disease subgroups that did not show homogeneous clinical features such as iRMD were evaluated according to expert opinion and the needs of patients for additional CS and NSAID use. However, few published studies have examined in detail compliance with b/tsDMARD during the pandemic to date [28].

Conclusions

In this observational study with a long follow-up period of 12 months, it was shown that approximately one-fifth of iRMD patients using b/tsDMARDs delayed their treatment due to the fear of COVID-19 infection in the first three months of the pandemic process, but with good communication with the patients, b/tsDMARD treatment was restarted and the 12-month drug retention status was quite high. The use of HCQ, the fact that bDMARD treatment is administered intravenously in the hospital, and the history of interrupting drugs in the first three months of the pandemic adversely affects the retention of b/tsDMARD treatment.

The results of this study suggest that the use of CS and the presence of ILD significantly increase the risk of COVID-19. Patients with RA and systemic vasculitis and those using csDMARD comedication and RTX seem to be at higher risk of catching COVID-19. It was observed that continuing biological and tsDMARD treatment other than RTX in iRMD patients did not increase the risk of COVID-19 infection. Conversely, TNFi treatment can reduce the risk of infection. These results suggest that continuing b/tsDMARD treatments in iRMD patients during the pandemic period is a logical treatment strategy that can be applied by preventing disease activation and reducing glucocorticoid requirement. It would be appropriate to evaluate RTX treatment on a patient basis.

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Authors' contributions

SG, YE, TI, IS, and FO contributed to the study design. SB, TY and IS contributed to data collection. All authors contributed to data analysis and/or interpretation, reviewed and critically revised the manuscript, approved the final draft, and are accountable for the accuracy and integrity of the work.

Data availability statement

Anonymized individual patient data will be shared upon request for research purposes dependent upon the nature of the request, the merit of the proposed research, the availability of the data, and its intended use.

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