original article

Clinical outcomes of patients with COVID-19 and inflammatory rheumatic diseases receiving biological/targeted therapy

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BACKGROUND: Anti-cytokine treatments are used in the treatment of severe COVID-19. Other studies have shown statistical significance with TNF inhibitors but not with other biological/ targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARD).

OBJECTIVES: Compare the rate of severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) infection and the course and incidence of COVID-19 infection in patients who received b/tsDMARD with control patients.

DESIGN: Analytical cross-sectional

SETTINGS: Tertiary care hospital

PATIENTS AND METHODS: All patients who applied to the rheumatology outpatient clinic between June 2020-March 2021 and received b/tsDMARD were included in the study. All patients with rheumatoid arthritis, psoriatic arthritis and spondyloarthritis who applied to the rheumatology outpatient clinic in the three months before March 2021 and did not receive b/tsDMARD were included as the control group. History of COVID-19 infection and treatments were recorded. Multivariate analysis was performed to assess factors associated with use of tumor necrosis factor (TNF) inhibitors and differences between specific biologic drugs.

MAIN OUTCOME MEASURES: Rate of COVID-19 disease among patients using biological/targeted synthetic therapy and non-biological/ targeted synthetic therapy. COVID-19 clinical outcomes (hospitalization, intensive care admission, mechanical ventilation and death).

SAMPLE SIZE: 553 in total; 341 received b/tsDMARD, 212 in the control group that did not receive b/tsDMARD.

RESULTS: One hundred patients (18%) had been infected with SARS-COV-2. The difference in SARS-COV-2 infection between b/tsDMARD and the control was statistically significant (13, 2% vs. 25, 9%, respectively) (P<.001). The hospital stays were longer in the controls (P<.001). Multinomial regression analysis revealed that COVID-19 negative patients were more likely to use tumor necrosis factor (TNF) inhibitors (OR: 2, 911; 95% CI: 1.727-4.908; P<.001) compared to COVID-19 positive participants. Multinomial logistic regression analysis indicated that non-hospitalized patients were more likely to use TNF inhibitors (OR: 11, 006; 95% CI: 3.447-35.138; P<.001) and there was no significant difference between b/tsDMARDs other than TNF inhibitors in frequency of hospitalization.

CONCLUSIONS: Patients who were medicated with b/tsDMARD were less likely to be infected with COVID-19 and be hospitalized due to the

infection. We have found that this effect was particularly dependent on the use of TNF inhibitors.

LIMITATIONS: Conducted in a single center and unable to provide a homogeneous study population.

CONFLICT OF INTEREST: None.

COVID-19 is a respiratory disease that was detected in Wuhan, China in December 2019, and has become a pandemic. The causative agent of COVID-19 is the SARS-COV-2 virus. It causes an inadequate immune response and uncontrolled inflammatory response by disrupting the normal immune response, especially in severely infected patients. The spike protein on SARS-CoV-2 binds to angiotensin receptor converting enzyme 2 (ACE2) in lung and intestinal epithelial cells. The spike protein is cleaved by host transmembrane serine protease 2, and the host cell membrane and viral envelope fuse together. This leads to activation of innate and adaptive immune cells in the infected host. Then cytokines and chemokines mediated by interleukin-6 (IL-6) and tumor necrosis factor (TNF) increase along with an increase in neutrophils, macrophages and formed T lymphocytes. For SARS-CoV, viral entry into the host cell not only increases TNF production, but also enhances the TNF converting enzyme-dependent release of ACE2 in the ectodomain, which facilitates viral entry.[1] The cytokine storm resulting from overproduction of pro-inflammatory cytokines is responsible for severe pneumonia, acute respiratory distress syndrome, multi-organ failure and organ damage.[2]

Clinical trials are ongoing to evaluate inflammatory cytokine-blocking agents that target IL-6 and IL-1β individually or in combination in the treatment of the cytokine storm.[3] TNF levels were higher in patients in intensive care units when compared with patients not in the intensive care unit.[4] In studies on agents that produce TNF inhibitors and Janus kinase inhibitors (JAK inhibitors) that are underway,[5] the use of TNF inhibitors shows promise as an immunomodulatory agent in the treatment of COVID-19.[6]

In rheumatic diseases, biological/targeted synthetic disease-modifying anti-rheumatic drugs(b/tsDMARD) play a major role in treatment algorithms[7] and these treatments may potentially increase the risk of infection.[8] On the other hand, biologic therapies may reduce the uncontrolled increased immune response to a viral infection, which could potentially have a protective effect.[9,10] In severe COVID-19 patients, the National Institutes of Health guideline includes tocilizumab, anakinra and some JAK inhibitors which are frequently used in rheumatology.[11,12] Also, b/tsDMARD such as TNF inhibitors and JAK inhibitors are currently being tested in the treatment of COVID-19.

Despite their known potential to increase susceptibility to infection, Gianfrencesco et al[13] demonstrated in a large-scale study that hospitalization odds were decreased in patients who were taking TNF inhibitors treatment. This result was not statistically significant with TNF inhibitors but not with other bDMARDs. In this study, we aimed to evaluate clinical presentation of COVID-19 in patients who underwent bDMARD therapy. Our aim in this study was to determine the rate and COVID-19 clinical outcomes (hospitalization, intensive care admission, mechanical ventilation and death) of COVID-19 among patients using biological/targeted synthetic therapy versus non-biological/targeted synthetic therapy.

PATIENTS AND METHODS

This analytical cross-sectional study included rheumatology patients who were followed up in the rheumatology clinic, Istanbul Health Sciences University Umraniye Training and Research Hospital, Turkey between June 2020 and March 2021. The inclusion criteria were as follows: a confirmed diagnosis of rheumatic disease for at least 3 months, including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, connective tissue disease, Familial Mediterranean fever, Behçet disease, or vasculitis. Exclusion criteria included pregnancy, and rheumatic diseases such as osteoarthritis and fibromyalgia. During this period, the evaluation of the patients who came to the medical examination was done in the hospital. However, the patients who did not come even though they had an examination appointment within the specified time were called by phone and evaluated by the same doctor.

The patients were grouped based on treatment received. The patients who received b/tsDMARD treatment were the biological group. b/tsDMARD treatments included in this study were TNF inhibitors (etanercept, adalimumab, infliximab, golimumab and certolizumab), IL-6 inhibitor (tocilizumab), IL-

17A inhibitor (secukinumab), CTLA4-Ig (abatacept), JAK inhibitors (tofacitinib), IL-1 antagonists (anakinra, canakinumab) and CD20 inhibitor (rituximab). Other patients who did not receive b/tsDMARD therapy served as a control group and were using conventional synthetic DMARD (csDMARD) or non-steroid anti-inflammatory drugs (NSAID). csDMARD consisted of methotrexate, leflunomide, hydroxychloroquine, colchicine and sulfasalazine. The patients who were receiving NSAIDs were classified as the noDMARD group within the control group. The study was approved by the Clinical Trials Ethics Committee (process no. 2020/412) and conducted in accordance with the Helsinki Declaration and Good Clinical Practices guidelines. Informed consent was obtained prior to inclusion.

Demographic and clinical features including age, sex, disease duration, medical history, data on current medication and comorbidities (hypertension, diabetes mellitus, cerebrovascular accidents, cardiovascular disease, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), malignancy, and asthma) were recorded. The drugs and the steroid doses, if any, were also noted.

A history of COVID-19 was obtained at the clinical controls of the patients from the control patients. The clinical symptoms and COVID-19 treatments of those with positive nasopharyngeal swabs and those diagnosed with COVID-19 according to the diagnosis guidelines of theTurkish Ministry of Health.[14] were recorded. Patients included in the study contacted by the investigators by telephone to determine if they were diagnosed with COVID-19 outside of their follow-up periods. Immunomodulatory or immunosuppressive drug usage during COVID-19 infection was recorded. The clinical features of COVID-19 infection, pharmacological treatment for COVID-19 management, presence of lung involvement and COVID-19 clinical outcome (hospitalization, intensive care admission, mechanical ventilation and death) were evaluated.

We calculated the sample size of the study based on a trial that evaluated the factors associated with hospitalization for COVID-19 in patients with rheumatic disease.[13] In that study, hospitalized patients were in the bDMARD group, while 24% of non-hospitalized patients were in the bDMARD group and the difference was significant ($P<.05$).[13] While Type I error is 0.05 and test power is 0.95, the minimum sample size required in each group was determined as 183 by G-Power version 3.0.10 (*https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower*).

IBM SPSS (Armonk, New York, United States: IBM Corp) version 20.0 was used to perform statistical analyses. Descriptive statistics are reported as mean (standard deviation) for continuous variables and as number and frequencies for binary and categorical variables. The comparison of these variables was conducted with Mann-Whitney U test for continuous variables, as the data distribution was non-parametric. Chi-square test was used for categorical variables. The chi-square test was also performed to compare presence of COVID-19, symptoms and the course of the disease between the biologic and control groups. Multinomial logistic regression analysis was used to obtain odds ratios and 95% confidence intervals to determine the association between individual biological drug and COVID-19 for the type of drug as a dependent variable. Similarly, investigation of the association between specific TNF inhibitors (i.e. infliximab, etanercept, etc.) and COVID-19 was performed using multinomial logistic regression analysis. After obtaining crude ORs and 95% CI, confounding factors (i.e. age, gender, use of steroids, presence of lung diseases such as COPD/ILD) were included in the regression analysis to obtain adjusted ORs and 95%CI. $P<.05$ was set as statistical significance.

RESULTS

Of 597 patients with rheumatic and musculoskeletal disease, 553 patients were included in this study. Forty-four patients were excluded, 14 because they refused to participate, 25 had osteoarthritis/fibromyalgia, and 5 could not be reached. Among the 553 patients, 341 (61.7%) received a b/tsDMARD for a mean of 60.86 (36.4) months (**Table 1**). The biologic group consisted of patients who were receiving only b/tsDMARD (n=210, 61. 6%) and a combination of b/tsDMARD and csDMARD (n=131, 38, 4%), whereas those who were receiving csDMARD (n=180, 84, 9%) and no DMARD (n=32, 15, 1%) were included in the control group. In the biologic group, the distribution of biologic drugs was 77.1% for TNF inhibitors, 6.2% for JAK inhibitors, 5.0% for anti-IL17A, 7.3% for rituximab, 1.5% for IL1 blockers, 1.5% for CTLA4 inhibitors, and 1.5% for IL-6 blockers. Patients who were receiving TNF inhibitors, were medicated with infliximab (3.8%), etanercept (18.8%), adalimumab (23.2%), golimumab (18.5%) and certolizumab pegol (12.9%).

One hundred patients (18%) had been infected with SARS-COV-2 . There was a statistically significant difference in SARS-COV-2 infection between the biologic group and controls in favor of the biologic group (13.2% vs. 25.9%, respectively) ($P<.001$).

Table 1. Demographic and clinical data (n=553).

	Biological drug group (n=341)	Control group (n=212)	P value	Overall (n=553)
Female/Male	171/170 (49.9/50.1)	139/73 (65.6/34.4)	**<.001**	310/243 56.1/43.9
Age (years)	47.3 (13.4)	50.4 (14.4)	**.010**	48.5 (13.9)
Disease duration (months)	128.71 (85.4)	77.96 (74.6)	**<.001**	109.3 (85.0)
Disease				
Rheumatoid arthritis	161 (47.2)	154 (72.6)	**<.001**	315 (57.0)
Spondyloarthropathies	120 (35.2)	25 (11.8)	**<.001**	145 (26.2)
Psoriatic arthritis	47 (13.8)	20 (9.4)	.142	67 (12.1)
Connective tissue disease	5 (1.5)	7 (3.3)	.795	12 (2.2)
Familial mediterranean fever/Behcet's disease/ vasculitis	9 (2.3)	6 (2.8)	.372	14 (2.5)
Seropositivity (positive for RF and anti-CCP)	75 (22.0)	89 (42)	**.032**	164 (29.7)
COVID	45 (13.1)	55 (25.9)	**<.001**	100 (18.8)
Use of steroids	116 (34.0)	125 (59.0)	**.001**	241 (43.6)
Comorbidities	134 (39.3)	72 (34.0)	.121	206 (37.3)
Diabetes mellitus	39 (11.4)	25 (11.8)	.892	64 (11.6)
Hypertension	72 (21.1)	42 (19.8)	.747	114 (20.6)
Cerebrovascular accidents	9 (2.6)	4 (1.9)	.775	13 (2.4)
Cardiovascular disease	20 (5.9)	11 (5.2)	.850	31 (5.6)
Chronic obstructive pulmonary disease/asthma /interstitial lung disease	19 (5.6)	13 (6.1)	.852	32 (5.8)
Chronic renal failure	5 (1.5)	1 (0.5)	.414	6 (1.1)
Malignancy	4 (1.2)	6 (2.8)	.193	10 (1.8)
Inflammatory bowel disease	17 (5.0)	3 (1.4)	**.034**	20 (3.6)
Rheumatologic medications				
Only b/tsDMARD	210 (61.6)	0 (0)	**<.001**	210 (38.0)
b/tsDMARD+csDMARD	131 (38.4)	0 (0)		131 (23.7)
Only csDMARD	0	180 (84.9)		180 (32.5)
NoDMARD	0	32 (15.1)		32 (5.2)

Data are n (%) except age: mean (SD). b/tsDMARD: Biological/ targeted synthetic disease-modifying anti-rheumatic drugs. csDMARD: Conventional synthetic disease-modifying anti-rheumatic drugs. RF: rheumatoid factor, anti-CCP: anti-citrullinated protein.

However, neither the course of disease nor the mortality rate (0.06% for biologic group and 0% for the controls (*P*=. 566) were different between the two groups (**Table 2**). COVID-19 positive patients in the biologic group (n=45) were receiving b/tsDMARD as monotherapy (n=28, 62.0%) and b/tsDMARD+csDMARD (n=17.4%). In the control group, 13 patients (23.6%) who were receiving noDMARD and 42 patients (76.4%) who were receiving csDMARD were diagnosed with COVID-19 (n=55).

Multinomial regression analysis revealed that COVID-19 negative patients were more likely to use TNF inhibitors (adjusted OR: 2, 911; 95% CI: 1.727-4.908; *P*<.001) compared to COVID-19 positive participants and multinomial regression analysis showed that patients not hospitalized were more likely to use TNF inhibitors (adjusted OR:11, 006; 95% CI: 3.447-35.138; *P*<.001) compared to hospitalized patients. There was no significant difference between b/tsDMARDs other than TNF inhibitors in terms of hospitalization (**Table 3**). To investigate the association of specific TNF inhibitors (i. e. infliximab, etanercept, etc.) with COVID-19 and hospitalization, the population was divided into two groups (patients receiving a TNF inhibitor and patients not receiving a TNF inhibitor) (**Table 4**). Differences in age, gender, and use of steroids were also statistically significant.

DISCUSSION

The COVID-19 pandemic has created important issues for rheumatologists and immunosuppressed patients with inflammatory rheumatic diseases, such as the effect of drugs used in the treatment on virus infection, and whether use of these drugs should continue during this era. In particular, our knowledge on whether the use of biological agents poses a risk or whether it is protective against severe respiratory failure due to hyper-inflammation in COVID-19 is not clear. In our study, which we planned considering these questions, we compared inflammatory rheumatologic patients who received biologic treatment with those who did not. We found that patients who were receiving biological drugs were less likely to be infected with SARS-COV-2 and to be hospitalized due to the disease than the controls. However, biological medications did not change the severity of symptoms or the course of the disease.

In a retrospective study by Gianfrancesco et al,[13] which included the largest number of COVID-19 positive patients with rheumatologic diseases, they showed that the use of b/tsDMARD reduced hospitalization and subgroup analysis showed that this effect was due to the use of TNF inhibitors. These results are in line with ours. We also have shown that the frequency of COVID-19 infection was lower in patients who were medicated with TNF inhibitors. TNF inhibitors are used in patients with severe autoimmune diseases such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and inflammatory bowel disease (IBD). Feldman

Table 2. Symptoms and the course of COVID-19 and previous rheumatologic medications (n=100).

	Biologic group (n=45)	Control group (n=55)	*P* value
Signs and symptoms			
Asymptomatic	4 (8.9)	6 (10.9)	.504
Fever	13 (28.9)	22 (40.0)	.246
Dyspnea	12 (26.7)	19 (34.5)	.515
Cough/sputum	22 (48.9)	24 (43.6)	.688
Myalgia/weakness	23 (51.1)	33 (60.0)	.421
Loss of appetite	10 (22.2)	5 (9.1)	.092
Arthralgia	15 (33.3)	19 (34.5)	.899
Headache	11 (24.4)	11 (20.0)	.594
Sore throat	5 (11.1)	9 (16.4)	.451
Vomiting	6 (13.6)	7 (12.7)	.894
Diarrhea	5 (11.1)	5 (9.1)	.738
Loss of smell	19 (42.2)	19 (34.5)	.431
Loss of taste	17 (37.8)	19 (34.5)	.738
Lung involvement	14 (4.1)	13 (23.2)	.292
Clinical course			
Hospitalization	11 (3.2)	13 (23.6)	**<.001**
Duration of hospital stay (days)	5.92±6.06	7.17±6.63	.599
ICU stay	2 (0.6)	0 (0)	.569
Mechanical ventilation	2 (4.7)	0 (0)	.113
Death	2 (0.6)	0 (0)	.200
COVID-19 medication			
Favipiravir	40 (88.9)	52 (96.3)	.240
Hydroxychloroquine	4 (9.3)	5 (9.4)	.982
Azithromycin	2 (4.7)	3 (5.7)	.825
Steroids	4 (9.3)	7 (13.2)	.550
Anti-cytokine-IVIG	1 (2.3)	3 (5.7)	.416
Antibiotics	10 (22.7)	11 (20.4)	.640

Data are n (%). ICU: intensive care unit. IVIG: intravenous immunoglobulin.

et al[10] were the first to report that TNF inhibitors therapy could be potentially beneficial in the treatment of COVID-19. These treatments inhibit TNF, the main cytokine in uncontrolled inflammation and cytokine release syndrome, and are effective in treating severe damage. Observational clinical data also support the potential impact of TNF inhibitors use.

In a meta-analysis comparing rheumatic diseases with the general population, it was reported that the use of TNF inhibitors reduced hospitalizations.[15] According to data obtained from the SECURE-IBD (a database of COVID-19 IBD patients; *https://covidibd.org/*), no relationship was found between severe COVID and use of TNF inhibitors may be protective against severe disease.[16] The PsoProtect study group reported that decreased use of TNF inhibitors increased hospitalization in patients.[17] In a different study, 77 autoimmune patients with COVID-19 using immunomodulatory therapy, none of the patients receiving TNF inhibitors treatment required ventilatory support or died.[18] On the other hand, there are other studies that report no difference in terms of hospitalization and mortality between the patients who were medicated with TNF inhibitors and those who were not.[19-21] These differences in the results may originate from the designs of the studies. Recently, there are case reports showing that the use of TNF inhibitors in various inflammatory diseases does not cause death and respiratory complications in COVID-19 and they have milder illness.[22-24] There are few case reports and observational studies on the use of TNF inhibitors for the treatment of COVID-19 in the acute phase.[25-27] Wang et al[15] showed the effect of advanced age and comorbidities such as hypertension or lung diseases on hospitalization in a meta-analysis. The fact that no difference was found in age and

Table 3. Multinomial logistic regression analysis for type of biological drug as the dependent variable (n=553).[a]

	Crude OR	95% CI	*P*	Adjusted OR[b]	95% CI	*P*
TNF inhibitor						
COVID-19 (-)	2.683	1.644- 4.379	<.001	2.911	1.727-4.908	**<.001**
Hospitalization (-)	11.907	4.243-33.414	<.001	11.006	3.447-35.138	**<.001**
JAK inhibitor						
COVID-19 (-)	1.462	0.471-4.535	.511	2.028	0.606-6.786	.251
Hospitalization (-)	NA	NA	NA	NA	NA	NA
IL-17A inhibitor						
COVID-19 (-)	1.118	0.35-3.575	.851	2.217	0.665-7.391	.195
Hospitalization (-)	4.465	0.538-37.170	.166	1.701	0.162-17.816	.658
Rituximab						
COVID-19 (-)	1.089	0.413-2.869	.863	2.701	0.946-7.712	.063
Hospitalization (-)	1.465	0.421-5.094	.548	4.405	0.952-20.393	.058
IL-1 inhibitor						
COVID-19 (-)	NA	NA	NA	NA	NA	NA
Hospitalization (-)	NA	NA	NA	NA	NA	NA
CTLA4 Ig						
COVID-19 (-)	1.376	0.15-12.579	.778	2.029	0.213-19.314	.538
Hospitalization (-)	1.116	0.114-10.944	.925	4.875	0.371-64.034	.228
IL6 inhibitor						
COVID-19 (-)	NA	NA	NA	NA	NA	NA
Hospitalization (-)	NA	NA	NA	NA	NA	NA

[a]Reference group: control group. TNF: tumor necrosis factor. JAK: Janus kinase. IL: Interleukin. [b]Adjusted for age. gender. lung diseases and use of steroids.

comorbidities between biologic group and control patients in our study suggests that the effects of these factors are similar in both groups. The use of anti-cytokine therapies in the treatment of COVID-19 is not a new idea. Although IL-6/ IL-1 inhibition is included in the treatment algorithm of our ministry in the current treatment of macrophage activation syndrome due to COVID-19,[28] the European League Against Rheumatism (EULAR) recommendations have reported that there is no solid evidence for the official use of both IL-6 and anakinra in treatment.[29] It was reported in the first randomized, controlled, phase 3 study with the IL6 inhibitor tocilizumab that COVID-19 patients did not differ in terms of clinical status and death control.[30] In the randomized controlled study of the CORIMUNO-ANA-1 study group, it was observed that anakinra did not improve the results in mild to moderate COVID-19 pneumonia patients.[31] In our study, no difference was found in hospitalization and COVID-19 status in patients using IL-1i and IL-6i. However, the number of patients in these subgroups was smaller than in other studies. Consistent with our results, there was no difference in hospitalization and intensive care stays with use of non-TNF biologic drugs in a meta-analysis by Wang et al.[15] The Global Rheumatology Alliance physician-reported registry study group found significantly worse results in rituximab and JAK inhibitors treatment compared to TNF inhibitors in the evaluation of COVID-19 in patients receiving b/tsDMARD treatment, and no relationship was found between abatacept and IL-6 inhibitors.[32] In our study, two patients died during the follow-up; one was under rituximab therapy. According to our results, rituximab did not have a statistically significant effect on the clinical presentation of COVID-19. This may be because our study included relatively fewer patients.

Contrary to these results with JAK inhibitors, EULAR recommendations state that the combined use of baricitinib with remdesivir may shorten the recovery period and accelerate improvement in the clinical condition.[29] It has also been reported that deaths due to COVID-19 in rheumatic patients increase with the use of rituximab and that use of rituximab increases the risk of pneumonia.[33,34]

In our study, we did not detect any difference in terms of the frequency of COVID-19 infection and hospitalization in b/tsDMARD drugs other than TNF inhibitors. In addition, we found that adalimumab, etanercept and golimumab among TNF inhibitors drugs had an effect on COVID-19 status, whereas adalimumab also reduced the hospitalization ratio. Therefore, our results indicate that adalimumab is more effective than other TNF inhibitors.

Table 4. Multinomial logistic regression analysis for each a tumor-necrosis factor inhibitor as the dependent variable.[a]

	OR	95% CI	*P*	Adjusted OR[b]	95% CI	*P*
Infliximab						
COVID-19 (-)	1.733	0.375-8.009	.481	1.669	0.356-7,816	.516
Hospitalization (-)	NA	NA	NA	NA	NA	NA
Etanercept						
COVID-19 (-)	2.566	1.118-5.885	**.026**	2.796	1.193-6.550	**.018**
Hospitalization (-)	9.947	1.297-76.275	**.027**	NA	NA	NA
Adalimumab						
COVID-19 (-)	2.237	1.094-4.574	**.027**	2.515	1.196-5.290-	**.015**
Hospitalization (-)	6.079	1.371-26.951	**.018**	5.657	1.160-27.596	**.032**
Golimumab						
COVID-19 (-)	2.993	1.237-7.243	**.015**	3.295	1.310-8.288	**.011**
Hospitalization (-)	3.158	0.894-11.157	.074	NA	NA	NA
Sertolizumab						
COVID-19 (-)	2.458	0.932-6.48	.069	1.803	0.290-11.222	.528
Hospitalization (-)	NA	NA	NA	NA	NA	NA

[a]Reference group: not receiving TNF inhibitors. [b]Adjusted for age. gender. lung diseases and use of steroids.

We found that the odds of being infected or hospitalized due to COVID-19 were lower in both b/tsDMARD as monotherapy and in combination with csDMARD compared to the noDMARD group. However, there was no difference between noDMARD and csDMARD groups. Similarly, Ferri et al[35] reported in their large study that the csDMARD had no effect on the prevalence of COVID-19. Therefore, we believe the effect of combination therapy (i. e. b/tsDMARD+ csDMARD) was mainly due to b/tsDMARD and TNF inhibitors. Many studies in the literature confirm our results on TNF inhibitors.[15-18]

This study had some limitations. First of all, we were unable to provide a homogeneous populations of patients receiving biological medications. Specifically, a few people were medicated with anti-IL1 and anti-IL6 and thus, we were unable to calculate ORs for these drugs. Similarly, only 3.3% of TNF inhibitor group were medicated with infliximab. Another limitation was that this study was conducted in a single center. In addition, during the study period, COVID-19 vaccination was not started in our country, so we do not have vaccination data.

There are also factors that may have caused bias in the results of the study. First, the biologics group were younger than the others, which may be important in the prognosis of COVID-19. Also, most of our patient population were diagnosed with chronic inflammatory arthritis, and the number of patients with vasculitis was fewer; those patients may have a worse prognosis. Additionally, patients receiving biologic therapy may have been more likely to pay attention to social distance, hygiene and mask rules than the other groups. Also, in our country some of the patients using biological drugs did not go to work during this period, so the possibility of COVID-19 exposure may have been decreased. Another bias is that some of the patients were seen face-to-face in the clinic and some were reached by phone, but there was also a group of patients who could not be reached so their information was missing. However, the rate of non-responders in our analysis was very low (0.09%). Another important issue is that the study was single-center and included patients from a certain socioeconomic and cultural level. Although it cannot be generalized to all rheumatic patients, it reflects our patient population.

In conclusion, we found that patients who were receiving biological drugs were less likely to be infected with SARS-COV-2 and be hospitalized. Among other biological drugs, anti-TNF drugs were significantly associated with lower odds of SARS-COV-2 infection and hospitalization. These associations were especially prominent with adalimumab. Our results may be useful in optimizing treatment management during the pandemic and encouraging patients to adhere to their treatments. In addition, the promising results on the use of biologic drugs such as TNF inhibitors in COVID-19 and the findings in some observational and case reports that they may be effective in the treatment of cytokine release syndrome due to COVID-19 have created a hope in the treatment of severe COVID. The results of prospective studies planned to clarify this matter are eagerly awaited.

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