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Letter to Editor

Clinical course and outcome of COVID-19 in patients with autoimmune inflammatory diseases under treatment with TNF inhibitors

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Dear Editor,

In the past two decades, tumor necrosis factor inhibitors (TNFis) have widely been used for treating of autoimmune inflammatory diseases (AID). TNF-α plays an important role in the protection against viruses, and patients treated with TNFis are at risk of viral infections.[1] It has been hypothesized that despite a higher risk of viral infection in patients with AID treated with TNFis, suppression of immune response with these medications can alleviate cytokine storm and lead to a better outcome.[2] Several studies reported a lower hospitalization rate, need to intensive care unit (ICU) care, and mortality in patients with AID on treatment with TNFis.[3-5] However, AID are nonhomogeneous group of diseases, and the variety of clinical symptoms and comorbidities, in addition to the various medications used to treat them, may lead to bias in these studies. The aim of this study was to compare the outcome of COVID-19 in TNFis treated and TNFis naïve patients with AID.

The COVID-19 AID (C19-AID) cohort is a prospective cohort started on 3 April 2020. Data of patients with AID who developed COVID-19 and being followed up in the clinics of Tabriz University of Medical Sciences (TUOMS) were entered in this cohort. Inclusion criteria in our study included the following: diagnosis of AID according to the clinical criteria, disease onset before COVID-19 outbreak, and age ≥ 16. Information about developing COVID-19 was obtained by telephone or direct interview and reviewing electronic medical records. COVID-19 was diagnosed according to the clinical symptoms consistent with COVID-19 and (i) positive polymerase chain reaction or (ii) chest computerized tomography scan findings of COVID-19 pneumonia and ruling out the other causes of pneumonia or having close contact with a definite case of COVID-19. COVID-19 outcome was assessed by hospitalization rate, need to ICU care, and mortality. The study protocol was approved by the Ethics Committee of TUOMS. Informed consent was obtained from the participants.

Statistical analysis was performed using SPSS software version 16.0 (SPSS Inc., USA). Comparisons between on TNFis and TNFis naïve patients were made by chi-squared test and independent samples *t* test. The predictive factors for hospitalization with *P* values < 0.1 in univariate analysis were included in a multivariate regression analysis. Covariates included in the model were sex, having ≥ 2 risk factors of COVID-19, type of AID, medications, and disease activity.

Two hundred and fifty-one patients with AID who developed COVID-19 were enrolled in the study. Forty-four patients were on TNFis and 207 patients were not on TNFis prior to COVID-19 diagnosis. We compared the risk factors and clinical manifestations of COVID-19 in patients on TNFis with TNFis naïve patients (Table 1). Age ≥ 65 in TNFis naïve group and smoking in the group on TNFis were significantly more common. Except for a higher frequency of anosmia in patients treated with TNFis, there were no significant differences in clinical manifestation of COVID-19 between the two groups (Table 1, Figure 1). Eighty-three patients were hospitalized. Demographic and clinical characteristics of hospitalized and outpatient COVID-19 patients are shown in supplementary file 1. Predictors of hospitalization in multivariate regression analysis were treatment

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Table 1. Comparison of demographic characteristics, symptoms and outcomes of COVID-19 in on TNFis and TNFis naïve patients with AID (N = 251)

Patients with COVID-19	On TNFis (n = 44)	TNFis naïve (n = 207)	*P* value*
Demographic characteristics			
Age (mean ± SD), years	41.8 ± 15.1	49.7 ± 13.7	**0.001**
Female (%)	25 (56.8)	152 (73.4)	**0.024**
Type of AID			**0.001**
RA (%)	14 (31.8)	108 (52.2)	
IBD (%)	14 (31.8)	21 (10.1)	
SLE and other CVD (%)	0 (0)	37 (17.9)	
SpA (%)	15 (34.1)	13 (6.3)	
Vasculitis (%)	1 (2.3)	21 (10.1)	
UIA and others (%)	0 (0)	7 (3.4)	
Risk factors of COVID-19			
Age ≥ 65 (%)	2 (4.5)	34 (16.4)	**0.027**
Obesity (BMI ≥ 30) (%)	11 (25.0)	63 (30.4)	0.324
Smoking (%)	9 (20.5)	12 (5.8)	**0.008**
Hypertension (%)	8 (18.2)	50 (24.2)	0.308
Diabetes (%)	3 (6.8)	29 (14.0)	0.054
Cardiac disease (%)	1 (2.2)	6 (2.9)	-
Pulmonary disease (%)	0	19 (9.2)	-
Chronic kidney disease (%)	1 (2.2)	12 (5.8)	-
Malignancy (%)	0	5 (2.4)	-
Clinical manifestations of COVID-19			
Myalgia (%)	38 (86.3)	172 (83.1)	0.414
Anosmia (%)	35 (79.5)	113 (54.6)	**0.003**
Malaise (%)	34 (77.3)	170 (82.1)	0.261
Fever (%)	32 (72.7)	141 (68.1)	0.386
Cough (%)	32 (72.7)	127 (61.4)	0.126
Taste loss (%)	25 (56.8)	103 (49.8)	0.243
Dyspnea (%)	24 (54.5)	100 (48.3)	0.322
Sore throat (%)	16 (36.4)	69 (33.3)	0.393
Diarrhea (%)	13 (29.5)	49 (23.7)	0.244
Rhinorrhea (%)	6 (13.6)	31 (15.0)	0.568
Pneumonia on chest CT (%)	28 (63.6)	137 (66.2)	0.579
Medications			
Prednisolone (%)	24 (54.5)	149 (70.0)	**0.020**
NSAIDs (%)	6 (13.6)	25 (12.1)	0.470
csDMARDs			
Hydroxychloroquine (%)	8 (18.2)	104 (50.2)	**0.001**
Methotrexate (%)	14 (31.8)	97 (46.9)	**0.048**
Sulfasalazine, mesalazine (%)	20 (45.5)	45 (21.7)	**0.002**
Leflunomide (%)	2 (4.5)	18 (8.7)	0.282
Immunosuppressants			
Azathioprine (%)	8 (18.2)	25 (12.1)	0.196
Mycophenolate mofetil (%)	2 (4.5)	14 (6.8)	0.441
Cyclophosphamide (%)	0	4 (1.9)	-
Calcineurin inhibitors (%)	2 (4.5)	2 (1.0)	-
Outcomes of COVID-19			
Hospitalization (%)	7 (15.9)	76 (36.7)	**0.005**
ICU care (%)	1 (2.3)	26 (12.6)	**-**
Mortality (%)	1 (2.3)	14 (6.8)	-

**P* values less than 0.05 were considered as statistically significant. AID, autoimmune inflammatory diseases; SD, standard deviation; TNFis, TNFα inhibitors; RA, Rheumatoid arthritis; IBD, Inflammatory bowel diseases; SLE, Systemic lupus erythematosus; CVD, collagen vascular diseases; SpA; Seronegative spondyloarthritis, BMI, body mass index; CT, computed tomography; NSAIDs, nonsteroidal anti-inflammatory drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; ICU, intensive care unit.

Table 2. Factors associated with hospitalization in patients with AID

Parameters	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value*	OR (95% CI)	*P* value**
Male sex	1.43 (0.79-2.58)	0.231		
COVID-19 risk factor ≥ 2	2.96 (1.64-5.32)	0.001	2.08 (1.08-3.99)	**0.028**
SpA and IBD versus others	0.122 (0.05-0.32)	0.001	0.22 (0.07-0.65)	**0.006**
Treatment with NSAIDs	2.09 (0.98-4.48)	0.056	3.43 (1.29-9.12)	**0.014**
Treatment with prednisolone	6.69 (3.03-14.77)	0.001	5.02 (2.11-11.95)	**0.001**
Treatment with csDMARDs	0.919 (0.49-1.73)	0.792		
Treatment with immunosuppressants	1.49 (0.79-2.81)	0.209		
Treatment with TNFis	0.33 (0.14-0.77)	0.010	0.62 (0.22-1.71)	0.353
Active disease at the time of COVID-19	2.13 (1.18-4.13)	0.024	1.58 (0.72-3.47)	0.260

*P values < 0.1 in univariate analysis were included in a multivariate regression
**P values < 0.05 were considered as statistically significant.
AID, autoimmune inflammatory diseases; OR, odds ratio; CI, confidence interval; SpA, seronegative spondyloarthritis; IBD, inflammatory bowel diseases; NSAIDs, nonsteroidal anti-inflammatory drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; TNFis, TNFα inhibitors; BMI, body mass index.

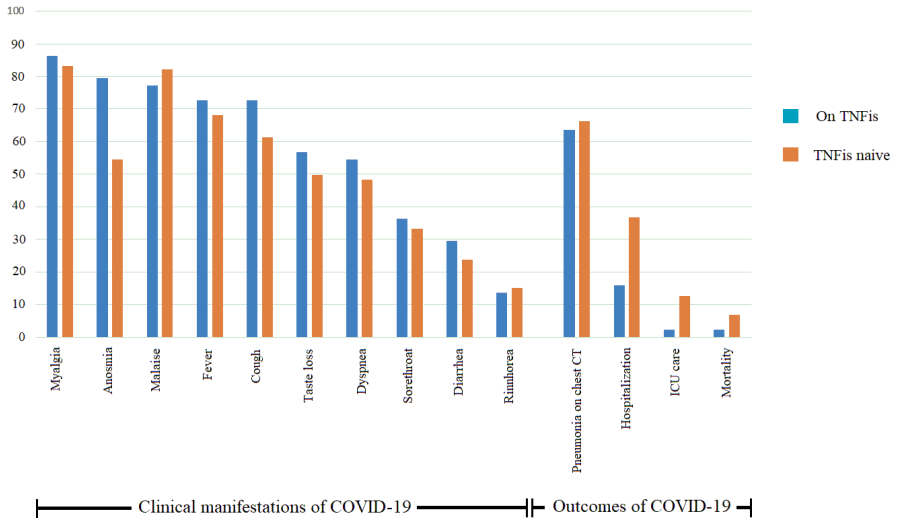

Figure 1. Clinical manifestations and outcomes of COVID-19 in patients with AID. AID, autoimmune diseases; TNFis, tumor necrosis factor inhibitors; CT, computed tomography; ICU, intensive care unit

with nonsteroidal anti-inflammatory drugs (NSAIDs), treatment with glucocorticoids and having COVID-19 risk factors ≥ 2 (Table 2). Hospitalization rate in patients with inflammatory bowel diseases and seronegative spondyloarthritis was less than the other AID group.

The data from this study showed that treatment with NSAIDs, treatment with glucocorticoids, and having COVID-19 risk factors ≥ 2 were independent risk factors for hospitalization in patients with AID. Being on TNFis was not an independent predictor of lower hospitalization rate.

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Authors' Contribution
Study design: LA, AKH, AMM. Data collection: LA, MB, KMSH, AKH. Data analysis: LA, AKH, AMM, MG. Interpretation of findings: LA, AKH, AMM, MG. Preparation of the manuscript: MB, AMM, AKH. All authors read and approved the final manuscript.

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Ethics Approval
The study was approved by the Institutional Review Board and Medical Ethics Committee of Tabriz University of Medical Sciences (ethics code: IR.TBZMED.REC.1399.988) and was conducted in accordance with the Helsinki Declaration for human research.

Conflict of Interest
The authors have no conflict of interest to declare.

Supplementary file
supplementary file contain Table S1.

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