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COVID-19 reinfection in rheumaic patients: Clinical characteristics and risk factors

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COVID-19 and autoimmune rheumatic diseases has been an interesting issue since the beginning of the COVID-19 pandemic. This survey was designed to study COVID-19 reinfection in autoimmune rheumatic patients and to find possible risk factors for reinfection related to autoimmune rheumatic diseases or their medications. In this cross-sectional survey, autoimmune rheumatic patients attending rheumatology clinics were interviewed to find rheumatic patients who had been infected by COVID-19. A group of patients who had been infected by COVID-19 just for one time and another group who had never been infected by COVID-19, were considered as control groups. Demographic and clinical characteristics of the three groups were compared. We found 15 patients (mean age: 45.33) who had been infected by COVID-19 two times. Rheumatoid arthritis was the most common disease (33.33%) and prednisolone was the most commonly used medication among these patients (80%). The mean interval between first and second infections was 8.53 months. We detected no significant differences for age, sex, type of autoimmune rheumatic disease, medications and comorbidities between our three group. Neither the type of autoimmune rheumatic disease, nor the type of medication used to treat it, was a risk factor for COVID-19 reinfection.

Keywords: COVID-19 reinfection; Autoimmune rheumatic diseases; Immune suppressive medications; Rheumatoid arthritis

Introduction

COVID-19 and autoimmune rheumatic diseases has been an important issue since the beginning of the COVID-19 pandemic. There is an agreement to the key emerging frontline role of rheumatologists in treating COVID-19. Increased possibility of being infected by COVID-19 or developing severe infection in autoimmune rheumatic patients due to the nature of their diseases and immunosuppressive medications, has raised serious concerns [1]. So far, no previous survey has studied COVID-19 re-infection in patients with autoimmune rheumatic diseases to find out whether these patients are more susceptible to COVID-19 reinfection or not. It is still unknown whether patients with rheumatic diseases produce sufficient levels of protective antibodies after COVID-19 infection to prevent reinfections at least for a short time in the future. Therefore, this study aimed to find possible risk factors of COVID-19 reinfection in autoimmune rheumatic patients.

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Materials and Methods

This cross-sectional study was conducted in 2021 between April and August. We interviewed patients with rheumatic diseases attending rheumatology clinics of Kermanshah University of Medical Sciences in Kermanshah, Iran, to find patients who had been infected by COVID-19 more than one time. Patients with positive real time polymerase chain reaction (RT-PCR) test, chest computed tomography (CT) scan findings consistent with corona-virus pneumonia or positive coronavirus serum antibodies were considered as COVID-19 infected patients. We included two other groups of rheumatic patients, as control group. The first group were the patients who had been infected by COVID-19 just one time and we included those with a history of COVID-19 infection six or more than six months prior to the interview. The second group were the patients who had never been infected by COVID-19 since the beginning of the pandemic. The sample size in the second group was about two and half times that of the first group.

The following data were collected from all participants: age, sex, comorbidities (diabetes mellitus, hypertension and chronic lung, heart and kidney diseases), type of autoimmune rheumatic disease including, rheumatoid arthritis (RA), seronegative spondyloarthritis (SPA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and vasculitis, medications including, glucocorticoids, conventional disease modifying anti-rheumatic drugs (cDMARDs), biologic DMARDs (bDMARDs) or targeted synthetic DMARDs. Additional data was obtained from the patients with a history of COVID-19 reinfection including: hospitalization, anti-rheumatic medications discontinuation during the course of COVID-19 infection and interval between the first and second infection. We divided disease types in to two main groups: inflammatory arthritis (RA and SPA) and collagen vascular diseases (SLE, SSc and vasculitis). Then, we compared the demographic and clinical data between the three groups to find possible risk factors for COVID-19 reinfection in autoimmune rheumatic patients.

At the time of conducting the study, vaccination against COVID-19 was not widely available in our country and none of the patients were vaccinated at the time of being infected by COVID-19. The local ethics committee approved the study (IR.KUMS.REC.1399.912). Informed written consent was obtained from the patients before enrollment.

Statistical analyses

SPSS version 25 (IBM) was used to analyze the data. Variables were reported as frequency, percentage, mean and standard deviation [SD]. One Way ANOVA test was used to compare quantitative variables (age) between the three groups. Chi-squared test and Fisher exact test were used to compare the categorical variables and to calculate P-values for qualitative variables. Statistical significance was defined as a P-value of less than 0.05.

Result

We found fifteen patients who had been infected by COVID-19 two times. Table 1 includes detailed demographic and clinical information of these patients. Their mean age was 45.33 with standard deviation of 11.04. All of them were female. Underlying rheumatic disease was RA in five patients, SPA in three patients SLE in three patients and SSc in four patients. Two patients hadanother underlying disease in addition to the autoimmune rheumatic disease (a 50-year-old female with hypertension and a 65-year-old male with diabetes mellitus). Fifteen patients wereusing prednisolone prior to COVID-19 infections (all of them were on the dosage ≤ 10 mg daily). Most of the patients were using at least one kindof cDMARDs (six patients Sulfasalazine, fivepatients Mycophenolate Mofetil, three patients Methotrexate, three patients Hydroxychloroquine, three patients Azathioprine and one patient Leflunomide). Two patients were on bDMARDs including, Adalimumab and Infliximab (each in one patient). Only one patient claimed that she discontinued her medications few months before COVID-19 infection and she was not using any anti-rheumatic medication prior to the COVID-19 infection.

The mean interval between first and second infections was 8.53 months (the shortest was 3 months and the longest was 12 months). Clinical manifestations and medications used for treating

Table 1. Characteristics of the 15 rheumatic patients who were infected by COVID-19 infection two times.

Patients	Age/Sex	Type of rheumatic disease	Rheumatic medications	Underlying diseases	Interval between two infections	Rheumatic medication discontinuation	Hospitalization
1	30/female	SSc	Prednisolone 2.5 mg/d, MM 2000 mg/d, Diltiazem, Pentoxifyline		6 months	MM was held for two weeks each time	No
2	29/female	SSc	Prednisolone 5 mg/d, MM 2000 mg/d, Diltiazem, Bosentan, Aspirin		5 months	She held all the drugs for two weeks	No
3	41/female	SSc	Prednisolone 5 mg/d, MM /d, Diltiazem, Bosentan		12 months	No drug	No
4	31/female	SSc	Prednisolone 5 mg/d, MM 1500mg/d, Diltiazem,		12 months	No drug	No
5	50/female	RA	Bosentan Prednisolone 5 mg/d, SSZ 500 mg/d	HTN	5 months	No drug was held	First time: No Second time: Yes (ICU)
6	59/female	RA	Prednisolone 10 mg/d, SSZ 1000 mg/d, leflunomide 20 mg/d, Infliximab 300 mg every 6-weeks		8 months	No drug was held	Fist time: Yes Second time: No
7	65/female	RA	Prednisolone 7.5mg/d, Azathioprine 100 mg/d, SSZ 1500 mg/d	DM, HTN	18 months	No drug	No
8	44/female	RA	No drug		7 months		No
9	50/female	RA	Prednisolone 5 mg/d, MTX 10 mg/weekly		8 months	No drug	No
10	43/female	SPA	Prednisolone 2.5 mg/d, MTX 12.5 mg/weekly, SSZ 1000 mg/d, Adalimumab 40 mg every 2-weeks		8 months	First infection: MTX and Adalimumab for 2 weeks Second infection: MTX for 3 weeks	No
11	56/female	SPA	Prior to first infection: MTX Prior to second infection: SSZ 1000mg/d		5 months	No drug	No
12	58/female	SPA	SSZ 1000mg/d		7 month	No drug	No
13	46/female	SLE	Prednisolone 5 mg/d, Hydroxychloroquine 200 mg/d, Azathioprine 50 mg/d		12 month	No drug	First time: No Second time: Yes
14	39/female	SLE	Prednisolone 7.5 mg/d, Hydroxychloroquine 200 mg/d, Azathioprine 50 mg/d,		3 months	No drug	No
15	39/female	SLE	Prednisolone 15 mg/d, Hydroxychloroquine 200 mg/d, MM 2000 mg/d,		12 months	No drug	No

MM: mycophenolate mofetil; SSZ: sulfasalazine; MTX, methotrexate; RA, rheumatoid arthritis; DM, diabetes; HTN, hypertension; SSc: systemic sclerosis; SPA: Spondyloarthropathy, SLE, systemic lupus erythematosus; UC: ulcerative colitis; PCR, polymerase chain reaction; CT, computerized tomography

COVID-19 infection was recorted for eachpatient. Three of the patients discontinued the immunosuppressive medication during COVID- 19 infection (two of them had SSc who hold Mycophenolate Mofetil and one had SPA who hold Methotrexate and Adalimumab). Most of the patients had mild infection which was managed in outpatient setting and did not need hospitalization, only three patients developed severe infection leading hospitalization (Two of these patients reported the second infection to be more severe). Table 2 contains information of the control groups (patients who were infected by COVID-19 one time (20 patients) and those who have never been infected (35 patients). Age, sex, type of autoimmune rheumatic diseases and comorbidities are reported. RA and SPA were the most common disease among the patients who have never been infected by COVID- 19 (34.28%). RA and SLE were the commonest diseases among those who were infected by COVID-19 just one time. Prednisolone was the most commonly used drug among the patients of both groups. Sulfasalazine was the most commonly used cDMARD among the patients who have never been infected by COVID- 19, followed by Methotrexate. Among the patients who were infected by COVID-19 just one time, Methotrexate was the most commonly used cDMARD followed by Sulfasalazine and Hydroxychloroquine.

Table 2. Characteristics of the rheumatic patients who were not infected by COVID-19 or who were infected just for one time (reported by number (%) for qualitative variables and mean, SD for quantitative variables).

Demographical and clinical variable	Patients who were not infected (N=35)	Patients who were infected one time (N=20)
Age (mean, SD)	46.68, 10.76	46.60, 10.54
Sex		
Female	32 (91.43)	17 (85)
Type of rheumatologic disease:		
Inflammatory arthritis:	24 (68.57)	11 (55)
Rheumatoid arthritis	12 (34.28)	6 (30)
Spondyloarthropathies	12 (34.28)	5 (25)
Collagen vascular diseases:	11 (31.43)	9 (45)
Systemic lupus erythematosus	8 (22.86)	6 (30)
Systemic sclerosis Vasculitis	2 (5.71)	2 (10)
	1 (2.86)	1 (5)
Anti-rheumatic medication:		
Prednisolone	30 (85.71)	18 (90)
dose ≤ 5 mg/d	25 (71.43)	14 (70)
5 mg< dose ≤10 mg/d	4 (11.43)	4 (20)
Conventional DMARDs:		
Hydroxychloroquine	11 (31.43)	4 (20)
Methotrexate	13 (37.14)	7 (35)
Sulfasalazine	15 (42.86)	4 (20)
Leflunomide	10 (28.57)	2 (10)
Azathioprine	6 (17.14)	3 (15)
Mycophenolatemofetile	1 (2.86)	2 (10)
Biologic DMARDs:	8 (22.86)	2 (10)
Adalimumab	5 (14.28)	2 (10)
Etanercept	2 (5.71)	0
Infliximab	1 (2.86)	0
Comorbidity:		
Diabetes Mellitus	1 (2.86)	5 (25)
Hypertension	3 (8.57)	0
Chronic lung, heart or kidney disease	0	0
COVID-19 diagnosis:		
Clinical manifestations and contact history		5 (25)
PCR		7 (35)
Chest CT scan infiltrates		11 (55)

SD, standard deviation; DMARD, disease modifying anti-rheumatic drug, PCR, plasma chane reaction; CT, computed tomography

Table 3 compares the demographic and clinical variables between the three groups. There were no significant differences in age, sex, type of autoimmune rheumatic disease, anti-rheumatic medications and comorbidities between the three groups.

Table 3. Variables compared between the three groups (reported by number (%) for qualitative variables and mean, SD for quantitative variables).

Variables	Patients infected by COVID-19 two times	Patients infected by COVID-19 one time	Patients who were not infected by COVID-19	P-value
Age (mean, SD)	45.33, 11.04	46.60, 10.54	46.68, 10.76	0.915
Sex				
Female	15 (100)	17 (85)	32 (91.43)	0.73
Type of rheumatologic disease:				
Inflammatory arthritis	8 (53.33)	11 (55)	24 (68.57)	0.47
Rheumatoid arthritis	5 (33.33)	6 (30)	12 (34.28)	0.95
Spondyloarthropathies	3 (20)	5 (25)	12 (34.28)	0.61
Collagen vascular diseases	7 (46.66)	9 (45)	11 (31.43)	0.47
Systemic lupus erythematosus	3 (20)	6 (30)	8 (22.86)	0.81
Systemic sclerosis	4 (26.67)	2 (10)	2 (5.71)	0.13
Vasculitis	0 (0)	1 (5)	1 (2.86)	
Anti-rheumatic medications:				
Prednisolone	12(80)	18 (90)	30 (85.71)	0.70
c DMARD only	12 (80)	15 (75)	27 (77.14)	0.89
b DMARD only	0 (0)	1 (5)	1 (2.86)	>0.99
cDMARD+bDMARD	2 (13.34)	1 (5)	7 (20)	0.36
Having underlying disease	2(13.34)	5 (25)	4 (11.43)	0.47

SD; standard deviation; cDMARD, conventional disease modifying anti-rheumatic drugs; bDMARDs, biologic DMARDs

Discussion

COVID-19 infection has been well studied in rheumatic patients, but as far as we know, no previous survey has studied COVID-19 reinfection in rheumatic patients. Previous studies about COVID-19 infection in rheumatic patients have revealed different results, some of them indicated there is no increased susceptibility to be infected by COVID-19 or for developing severe infection in rheumatic patients [2-4]. But some other studies claimed that having anautoimmune rheumatic diseases [5] or using anti-rheumatic medications such as biologic DMARDs [6] and prednisolone ≥ 10 mg daily [7], would be a risk factor for COVID-19 infection or hospitalization related to it.

Based on the current knowledge on COVID-19 infection, healthy individuals produce protective antibodies against coronavirus about two or three weeks after being infected. This leads to temporary immunity against the disease which often lasts for about six months [8]. Shenoy et al. studied 50 patients with autoimmune rheumatic diseases and revealed that antibody protection after COVID-19 infection is adequate in these patients and similar to healthy individuals [9]. Results of our study isconsistent with these findings. Since reverse transcription polymerase chain reaction (RT-PCR) may be false positive due to the shedding of the virus genetic material in the respiratory secretions after first COVID-19 infection [10], we included patients who developed second COVID-19 infection more than three months aftertheir first infection and whose symptoms of the first COVID-19 infection had completely subsided. The mean interval between first and second infection in

our patients was 8.5 months that shows patients with rheumatic diseases have developed adequate immunity post COVID-19 infection (similar to healthy individuals).

When we compared three studied groups, we found no significant differences for demographic and clinical variables. Different types of autoimmune rheumatic diseases were distributed evenly between the three groups and type of disease was not a risk factor for reinfection. We also compared the three groups in terms of medications and observed differences were not statistically significant. Neither prednisolone, nor cDMARDs, bDMARDs, cDMARDs + bDMARDs was a risk factor of reinfection by COVID-19. Though, we should mention that all of our patients were on prednisolone ≤ 10 mg/d and previous studieshave shown increased risk of infection for higher doses of prednisolone [7]. In fact, without genomic assays in some cases it is difficult to distinguish between COVID-19 reinfection, relapse and PCR re-positivity. Yahav et al. recommended interval more than 90 days for reinfection [11], in this survey the interval between two infections was more than 90 days in all of the cases. Therefore, the results of this study on reinfection with COVID-19 in rheumatic patients can be reliable. This study is the first COVID-19 reinfection survey in rheumatic patients. And we considered two control groups to compare the type of auto-immune rheumatic diseases and anti-rheumatic medications in order to find the possible risk factors for reinfection of COVID-19 in these patients. The main limitation to this study was small size of the groups, The main reason is that COVID-19 reinfection is relatively rare and it was hard to find rheumatic patients with reinfection of COVID-19. Also in this study, serological examination was not performed to determine the titer of protective antibody against COVID-19, in addition we did not evaluate viral genome sequence to determine recurrence with the same viral strain or reinfection with other species of COVID-19 because genotypic assays are time and resource consuming. The population in each group is not similar and this could be considered as another limitation.

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Conflict of interest

The authors declare no conflict of interests.

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