COVID-19 among Rheumatoid Arthritis Patients on Immunosuppressive Therapy During the First Wave of the COVID-19 Pandemic: a Prospective Comparative Study

Amgad M. Rabia[1], Samar A. Amer[2,3],Hosam M Dawod[4,5] ,Youmna A. Amer[6]

[1]*Head of Drug Discovery & Clinical Research Department, Dikernis General Hospital (DGH), Dakahlia Governorate, Egypt*
[2]*Public Health and Community Medicine Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt.*
[3]*Membership at Royal Colleague of General Practice [INT], London, United Kingdom.*
[4]*Tropical Medicine Department, Faculty of Medicine, Zagazig University, Egypt.*
[5]*Consultant Gastroentrology, Ministry Of Health, Sultanate of Oman*
[6]*Rheumatology and Rehabilitation Department, faculty of medicine, Zagazig University*

Corresponding Author
Hosam M Dawod

Mobile:
00968 71583895,
002 01113008201

E mail:
hosamgastro@yahoo.com

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Background and aim of the work: COVID-19 has multiple challenges among risky cases like rheumatoid arthritis patients. So, this study was done to look for COVID-19 in patients with rheumatoid arthritis and compare the severity and outcome of COVID-19 in rheumatoid arthritis patients to those in other groups.

Patients and Methods: the prospective comparative study included 146 randomly selected patients attending Zagazig University Hospital in Egypt ,who were treated by the Egyptian Ministry of Health and Population protocol for COVID-19, and the disease-modifying antirheumatic drugs (DMARDs)who fulfilled the selection criteria to be recruited into three groups: rheumatoid arthritis (RA) patients; rheumatoid arthritis with COVID-19 patients (RA-COVID); and a COVID-19 (COVID-19) group.

Results: the mean age of the studied group was 50 years old. The three studied groups showed no statistically significant difference ($p > 0.05$) as regards age, sex, level of education, and marital status. But there was a statistically significant difference between groups regarding occupation and special habits in the form of hashish smoking. There was no marked difference in COVID-19 symptoms between group II and group III. The mean of the Modified Health Assessment Questionnaire (MHAQ) was 5.5 in RA group versus 8 in RA-COVID-19 group ,with statistically significant difference between group I and II as regard DAS28. The duration from being diagnosed with COVID-19 till recovery was significantly higher in RA-COVID-19 cases compared to COVID-19. RA-COVI-19 group did tend toward higher hospital admission rates (OR 0.81; 95% CI 0.35-0.88; $p = 0.03$).

Conclusion: COVID-19 is accompanied by non-significant worsening of symptoms in RA patients on DMARDs, except the admission rates. More research into expanding cases is required .

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has quickly become a pandemic virus that has resulted in severe morbidity and mortality around the world. Since the outbreak of COVID-19 in late 2019, global healthcare systems have faced numerous problems, ranging from many patients to a shortage of approved therapy alternatives. A lot of work has been done around the world to find effective ways to treat the virus **[1]**.

According to the World Health Organization, there is insufficient evidence to recommend any specific COVID-19 treatment for patients who have been diagnosed with COVID-19 **[2]**. RA is a T-cell and B-cell-mediated autoimmune

disease that primarily affects the joints but can also cause systemic symptoms **[3].** The profile of RA includes increased levels of proinflammatory cytokines, tumor necrosis factor (TNF) and interleukin (IL6) **[4]**, which is similar to the profile of COVID-19 **[5]**, as disease severity of COVID-19 was correlated with hypercytokinaemia, characterized by increased serum IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), monocyte chemoattractant protein 1, and granulocyte chemoattractant protein 1 **[6]**.

People with rheumatic and musculoskeletal diseases have been impacted during this pandemic through their greater risk of infection due to immune dysregulation, comorbidities, and immune modulating treatments **[7]**. At the same time, many of these immune modulating treatments (e.g., hydroxychloroquine [HCQ], glucocorticoids [GCs], interleukin1 [IL1], IL6 inhibitors, JAK inhibitors) are being tested to prevent or treat COVID-19 **[8]**, which have caused some confusion and concerns about the actual risks posed to individuals with rheumatic and musculoskeletal diseases **[9]**. Also, the available data on COVID19 infection rates and outcomes among patients receiving disease-modifying antirheumatic drugs (DMARDs) for rheumatoid arthritis are quite reassuring **[10]**. To date, data on the epidemiology of COVID-19 in rheumatoid arthritis patients is still scarce.

Therefore, this study was conducted to study COVID-19 severity and outcome among rheumatoid arthritis patients, including hospitalization, ICU admission, and mortality compared to others.

PATIENTS AND METHODS

Study design and setting:

A prospective comparative study was undertaken on 146 patients at Zagazig University Hospitals from July to December 2020 .Protocols from the Egyptian Ministry of Health and Population were used to treat the people who took part in the study.

Participants:

They were divided into 3 groups: **Group I**: Included 52 patients suffering from RA,**Group II** included 44 patients suffering from RA with COVID-19, **Group III** included 50 COVID-19 patients.

The RA with COVID-19 cohort included all patients who were 18 years of age or older, had a pre-existing diagnosis of RA, and were diagnosed with COVID-19 anytime from January 20, 2020 to December 2020. The diagnosis of RA was based on the 2010 ACR/EULAR criteria for RA **[11],** and the diagnosis of COVID-19 was based on clinical findings and SARS-CoV-2 polymerase chain reaction (PCR) positivity. The comparison group was made up of any adult without a known history of RA who was diagnosed with COVID-19 between January 20, 2020 and December 20, 2020.

Instruments and tools for data collection:

- Demographic characteristics (age, sex, level of education, marital status, special habits, and Occupation).
- The practice of preventive measurement (Hygienic hands wash, safe space more than two meter, surfaces disinfectants, and wearing masks).
- **Data on RA-related parameters:**

1. The disease's duration,
2. The clinical evaluation:

- The Modified Health Assessment Questionnaire (MHAQ) is a self-reported outcome questionnaire that helps doctors figure out how well RA patients can do their jobs. It included questions about the perceived patient's satisfaction regarding the same daily activities as well as the change in the degree of difficulty **[12].**
- The disease activity of RA patients was calculated using the Modified Disease Activity Score (DAS-28) **[13],** equation with the number of swollen joints (NSJ), number of tender joints (NTJ), ESR, and patient response on visual analogue using the Global Assessment (PGA) of disease activity. DAS classified A patients as mild (2.4), moderate (2.5-3.7), or severe (> 3.7) **[14].**

3. The RA treatment protocol's: Medication for RA patients from medical records included conventional synthetic DMARDs as methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide.

- **COVID-19 symptoms and outcomes**

1. The acute COVID-19 symptoms.

2. COVID-19 outcomes included mortality, hospitalization, intensive care unit-ICU admission, mechanical ventilation, severe COVID-19 (a composite of mechanical ventilation and mortality), and acute respiratory distress syndrome-ARDS. All examined outcomes were assessed within 30 days after the COVID-19 diagnosis.
3. The COVID 19 treatment protocol's; a uniform prescription form was produced and issued with the documented treatment protocol. The prescription called for hydroxychloroquine to be taken for five days, starting with 400 mg twice a day on day one and then 200 mg twice a day for the next four days. Patients with renal or hepatic impairment should not modify their dose. Zinc sulphate, 60 mg orally once daily for 5 days, paracetamol, and an antihistamine were also included in the prescription. The antibiotic azithromycin was not included in the prescription. Follow up within 3-7 days after starting therapy.

Data analysis:

The outcome variables included reported treatment protocol outcomes such as the percentages of patients who were hospitalized, admitted to the ICU, or died. IBM SPSS Statistics version 21 was used to analyze all the data. Considerations on morality Following a description of the study, the treating physician got informed permission from the participants. Those who refused to participate in the trial were removed from the study and were given standard supportive care instead. All information gathered will be kept private and used solely for the purpose of the study. Patients who were unstable at the time of presentation or who showed clinical progression/deterioration on days 3-7 were referred to the hospital, and the study team followed up on their progress.

RESULTS

This study included 146 randomly selected patients attending Zagazig university hospitals. The socio-demographic characteristics of the participants are shown in **[table 1**]. The three studied groups were matched and showed no statistically significant difference ($p > 0.05$) as regards age, sex, level of education, and marital status. But there was a statistically significant difference between the groups in terms of occupation and smoking hashish.

There was a statistically significant difference ($p < 0.05$) as regards the practice of preventive measurements (including safe spacing greater than 2 meters, applying surface disinfectants, and always wearing masks) among the studied groups except hygienic hands wash to be significantly higher among the RA group and Group II (RA and COVID19) in comparison to COVID - 19 infected cases **[table 2].**

There was an analytical difference, as regards the acute symptoms of COVID-19 among the studied groups, between the studied RA group (Group 1) in comparison with the other groups; COVID-19 cases (COVID-19 only and Rheumatoid with COVID-19). There was no marked difference in symptoms between group II and group III but both had significantly more symptoms than RA group, in other terms all symptoms increase with COVID-19 infection (group 2 and 3) except fatigue (non-significant). COVID-19 infection is accompanied by significant worsening of symptoms in RA with COVID-19 group compared to the COVID-19 group. RA with COVID-19 (group II) patients suffered from 38 (86.4%) muscle pain, 40(90.9%) fatigue, and 36 (81.8%) sore throat. COVID-19 group had presented with more fever 46 (92.0%), headaches 34 (68.0%) and skin rash 36(72%) than combined disease **[Table 3],** after adjusting for gender and occupation with binary logistic regression models, there were statistically significant differences between groups 2 and 3, RA with COVID-19 group did tend toward higher hospital admission rates (OR 0.81, 95% CI 0.35-0.88, $p = 0.03$) **[table 4].** As regards the clinical assessment of RA, The mean of MHAQ was 5.5 in RA group versus 8 in RA-COVID-19 group ,with statistically significant difference between group I and II as regard DAS28, the time from diagnosis to recovery was significantly shorter than in COVID-19 cases **[table 5].** As regards the medications and their outcomes **[table 6].**

Table (1): The Demographic Characteristics of the Studied Groups.

	Group I RA F (%) No=52	Group II RA+COVID19 F (%) N0= 44	Group III COVID19 F (%) No=50	P
Age (y)				
mean±SD	38.3±8.6	37.8±7.5	42.1±17.3	0.45
range	22-57	44-78	12-79	
Sex				
Females	36(69.2)	32(72.7)	22(44.0)	3.57
Males	16(30.8)	12(27.2)	28(56.0)	(0.17)
Education				
Illiterate	12(23.1)	8(18.0)	4(8.0)	7.54
Read, write/ primary	10(19.2)	10(40.0)	6(12.0)	(0.23)
Secondary /high	10(19.2)	18(40.9)	16(32.0)	
Universities	20(38.5)	8(18.0)	24(48.0)	
Occupation				
Unemployment	20(38.5)	10(22.7)	6(24.0)	
Medical field	0(0.0)	4(9.1)	9(34.6)	0.002*
Other fields	28(53.8)	22(50.0)	5(20.0)	
Retired	4(7.7)	499.1)	5(20.0)	
Marital status				
Single	6(11.5)	0(0.0)	10(20.0)	5.10 (0.28)
Married	36(69.2)	36(81.8)	30(60.0)	
Divorced	10(19.2)	8(18.2)	10(20.0)	
Special habits				
Cigarettes Smoking	14(26.9)	12(27.7)	14(28.0)	0.001(0.99)
Shisha	10(19.2)	10(22.7)	4(8.0)	2.078(0.35)
Alcohol	0(0.0)	2(4.5)	0(0.0)	0.39
Hashish	0(0.0)	10(20.0)	4(8.0)	0.03*
Contact history				
Don't know	48(92.3)	30(68.2)	28(56.0)	0.000*
Contact to contact	3(5.8)	2(4.5)	6(12.0)	
Contact to confirmed case	1(1,9)	12(27.3)	16(32.0)	
Disease duration of the RA(y)				
Median (mean±SD)	6(6.7±4.6)	5(5.±3.5)		0.16
Range	1-20	(1-12)		
COVID-19 duration since diagnosis (d)				
mean±SD		7±2.1	6.9 ± 1.9	0.44

*p <0.05 there was a statistically significant difference

Table (2): The Practice of preventive measurements among the studied groups.

	Group I RA F (%) No=52	Group II RA+COVID19 F (%) N0= 44	Group III COVID19 F (%) No=50	P
Hygienic hands wash				
Rare	1(1.9)	2(4.5)	0(0.0)	0.85
Sometimes	19(36.5)	18(40.9)	18(36.0)	
Always	33(63.5)	24(54.5)	32(64.0)	
Safe space (>2meter)				
Rare	2(3.8)	0(0.0)	12(24.0)	0.001*
Sometimes	20(38.5)	20(45.5)	30(60.0)	
Always	30(57.7)	24(54.5)	8(16.0)	
Surfaces disinfectants				
Rare	8(15.4)	8(18.8)	4(8.0)	0.02*
Sometimes	16(30.7)	26(59.1)	24(24.0)	
Always	28(53.8)	10(20.0)	22(44.0)	
Wearing masks				
Rare	8(1.5)	36(81.8)	18(36.0)	0.0001*
Sometimes	12(23.1)	4(13.6)	20(40.0)	
Always	32(61.5)	2(4.5)	12(24.0)	

*p <0.05 there was a statistically significant difference

Table (3): The acute symptoms of COVID-19 among the studied groups.

	Group I RA F (%) No=52	Group II RA+COVID19 F (%) N0= 44	Group III COVID19 F (%) No=50	P
No symptoms	1(1.9)	4(9.1)	4(8.0)	(0.30)
Fever	0(0.0)	38(86.4)	46(92.0)	<0.00001*
Headache	3(5.8)	26(59.1)	34(68.0)	< 0.00001*
Cough	6 (11.3)	32(72.7)	38(76.0)	<0.00001*
Difficulty breathing	0 (0.0)	42(95.5)	48(96.0)	<0.00001*
Sore throat	2(4.0)	36(81.8)	30(60.0)	<0.00001*
Congestion	0(0.0)	16 (36.4)	26(52.0)	0.03*
Fatigue	40(76.9)	40(90.9)	42(84.0)	0.18
Muscle pain	20(38.5)	38(86.4)	38(76.0)	<0.00001*
Diarrheas	7(13.4)	34(77.3)	36(72.0)	<0.00001*
Nausea /vomiting	6(11.5)	26(59.1)	28(56.0)	<0.00001*
Skin rash or lesion	0(0.0)	22(50.0)	36(72.0)	<0.00001*
Conjunctivitis	3(5.8)	14(56.0)	12(48.0)	0.004*

*p <0.05 there was a statistically significant difference

Table (4): COVID-19 complication and outcome among the studied groups.

	Group II RA+COVID19 F (%) N0= 44	Group III COVID19 F (%) No=50	P
Respiratory distress (>30 breath/min)	33(75.0)	36(72.0)	0.56
Oxygen saturation < 93%	28(63.6)	26(52.0)	0.19
Respiratory failure	3(6.8)	2(4.0)	0.82
Septic shock	0(0.0)	0(0.0)	---
Non -respiratory failure	0(0.0)	0(0.0)	---
Hospitalization	20(45.5)	13(26.0)	0.04*
ICU admission	1(2.27)	3(6.0)	0.26
Death	1(2.27)	3(6.0)	0.26
Duration from diagnosed COVID19 till recovery (days) **Median (mean±SD)** **Range (days)**	 16(17.8±8.4) (6-30)	 12(12.2±4.9) (9-32)	 136.6 (0.00*)

*p <0.05 there was a statistically significant difference / ICU (intensive care unit)

Table (5): The clinical assessment of Rheumatoid arthritis among the studied groups.

	Group I RA F (%) No=52	Group II RA+COVID19 F (%) N0= 44	Group III COVID-19 F (%) No=50	P
MHAQ Median (mean±SD)	 5.5 7.6±6.2	 8 8.8±5.3	 2 2.0±1.8	 (0.02*)
DAS-28 Median (mean±SD)	 3(3.1±0.8)	 4(3.6±0.5)		 (0.00*)
mild moderate Sever	12(23.1) 22(42.3) 18(34.6)	0(0.0) 18(40.9) 26(59.1)		

*p <0.05 there was a statistically significant difference

Table (6): The Frequency Distribution of Medications among the studied groups.

	Group I RA F (%) No=52	Group II RA+COVID-19 F (%) N0= 44	Group III COVID-19 F (%) No=50	P
ClexaneHeparin	0(0.0)	40(90.9)	14(56.0)	<0.00001*
Ceftriaxone	0(0.0)	16(36.4))	30(60.0)	<0.00001*
Iverzine	0(0.0)	10(22.7)	18 (36.0)	0.0001*
Zithromax	0(0.0)	18 (40.9)	38(76.0)	<0.00001*
Multivitamin	18(34.6)	32(72.7)	36(72.0)	<0.0001*
Vitamin C	2(3.8)	32(72.7)	50(100.0)	<0.00001*
Zinc	0(0.0)	40(90.9)	48(96.0)	<0.00001*
Vitamin B	6(11.5)	40(90.9)	44(88.0)	<0.00001*
Corticosteroid				
Low	28(53.8)	4(9.1)	36(72.0)	0.000031*
High dose	4(7.7)	42(84.0)	8(0.16)	
Pain Killer				
Aspirin	٠ (0.0)	2(4.5)	12(24.0)	0.00*
Paracetamol	١٢(23.1)	٤٠(8.0)	٣٨ (76.0)	0.00*
NSAID	16(30.8)	١٥(8.0)	12(48.0)	0.00*
DMARDS				
Methotrexate	44(84.6)	20(45.5)	0(0.0)	<0.00001
Colosalazine	16(30.8)	19(76.0)	٠(0.0)	0.00*
Arthfree	18(34.6)	٧(15.9)	٠(0.0)	0.00*
Hydroxychloroquine (HCQ)	46 (88.5)	44(100.0)	26 (52.0)	<0.00001*
Hydroxychloroquine Dose	400mg	400 (400-2000)mg	400 (0-1200)	
Side effects from HCQ				
No	40(76.9)	31(70.5)	30(60.0)	
Eye complications	6(11.5)	4(9.0)	0(0.0)	
Hyperpigmentation's	6(11.5)	5(11.4)	0(0.0)	0.00*
Cardiac complications	0(0.0)	0(0.0)	2(4.0)	
Others	0(0.0)	2(4.5)	18(36.0)	

* $p < 0.05$ there was a statistically significant difference

DISCUSSION

Both healthy people and those with chronic illnesses are susceptible to infection during the ongoing COVID-19 pandemic. 146 people were enrolled in this trial. 50 patients had COVID 19, age, sex, and comorbidity matched, and 44 of them had RA with COVID 19, were on DMARDs. They received the treatment plan prescribed by the Egyptian Ministry of Health and Population and went back to the clinics three to seven days after beginning the medication.

The practice of preventive measurements except hygienic measurements were significantly higher among RA patients either with or without COVID-19, compared to COVID-19 cases alone. In agreement with another study **[15]**. This may be attributed to the critical element is to guarantee honest, truthful communication with patients. Rheumatologists who are assisting patients with RMDs must make them feel supported because they are likely to be apprehensive. As recently acknowledged in the provisional recommendations of the European League Against Rheumatism (EULAR) **[16]**.

Most infected people experience, minor symptoms including headaches, fever, tiredness, and sore throat. Because of a pathogenic host response that results in a state of intense inflammation and harm to multiple organs, some infected persons become sicker and sicker over time.

As regards the main outcomes:

The Respiratory distress (>30 breath/min) was recorded in 72% of cases of non-RA COVID and 75% cases of RA with COVID19, respectively. However, there was no statistically significant difference in the risk of most events (mortality, ICU admission, mechanical ventilation, and

ischemic stroke), which is in line with other studies' findings **[17,18]**. This may be attributed to the effect of HCQ, is used to prevent endosome-lysosome system acidification and to reduce proinflammatory cytokines **[19]**. Although the therapeutic effectiveness of HCQ in COVID-19 is still debatable, some investigations demonstrated a benefit, other studies provided contradictory findings **[20]**. There is no evidence that people with RMDs, including those taking DMARDs, are more likely to get COVID-19 or that they will have a worse outcome if they do get it **[21-23]**.

In that study, England et al. discovered that RA was linked to a higher risk of mortality using the US Veterans Affairs COVID-19 shared database. This Disparities in study populations could be the cause of this gap (England et al. study consisted primarily of older males, consistent with the demographic profile of the Veterans Affairs **[24]**, whereas the current study consisted primarily of females, consistent with the general epidemiology of RA.

The SARS-CoV-2 infection is accompanied by non-significant worsening of symptoms in RA patients on DMARDs, except the admission rates, this may be attributed to that 42(84.0%) of cases use moderate-to-high-dose corticosteroid, which was frequently used in RA patients that increases the risk of hospitalization **[22]**.

As regards the management protocols:

The frequency of administration of HCQ was 44(100.0%) among Group II (RA+COVID19), while in only COVID-19 cases was only 26 (52.0%) of average dose 400 in mg in both and ranged from (0 to 1200 mg) according to the treatment plan prescribed by the Egyptian Ministry of Health and Population. Recent studies on clinical trials utilizing HCQ and chloroquine were analyzed by Chowdhury et al. They discovered that 5/7 completed clinical trials had successful results **[25]**. Only two studies had provided information on RA and COVID-19 before this one **[24,26]**. Our findings agree with those of Raiker et al. **[26]** but disagree with those of England et al. **[24]**.

Anti-inflammatory medications may help those patients. This result is thought to be caused by hyperinflammation, which underlying the pathophysiology of severe COVID-19. They might not experience the virus-induced cytokine storm syndrome because of their immunocompromised state. Prednisone, methylprednisolone, and dexamethasone are examples of glucocorticoids, while methotrexate and hydroxychloroquine are examples of DMARDs. Available transcriptome data, including RNA-seq and Gene Chip human genome arrays, demonstrate that glucocorticoids (prednisone, methylprednisolone, and dexamethasone) and some DMARDs **[27]**.

The medication side effect was significantly higher among the COVID-19 only cases to in 20(40%) of cases which may be attributed the to the effect of different medication of different doses, (48.0%) on NSADI, 48(96.0%) Zinc, 38 (76.0%) Paracetamol, 50(100.0%) Vitamin C, 38(76.0%) Zithromax, 36(72.0%) low dose corticosteroids, and 26 (52.0%) low dose Corticosteroid or may be attributed to the effect of COVID-19. Further detailed studies are required.

Strength and limitations:

The conclusion of the causation of the outcome of COVID-19 among those patients would be implied by the cross-sectional design of this study and the potentially brief duration of evaluation. However, it might be claimed that this study is one of the few studies to focus on RA patients during the COVID-19 pandemic in Egypt. Large-scale longitudinal research in the future would be necessary. Lack of multicentricity, which would restrict the generalizability of results, was another issue.

CONCLUSION

The covid-19 is accompanied by non-significant worsening of symptoms in RA patients on DMARDs, except the admission rates. More research into expanding cases is required. The practice of preventive measurements except hygienic measurements were significantly higher among RA patients.

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Conflicts of interest: No conflict of interest.

HIGHLIGHTS

1- Coronavirus disease 2019 (COVID-19) has quickly become a pandemic virus that has resulted in severe morbidity and mortality around the world.

2- Rheumatoid arthritis (RA) is a chronic autoimmune and inflammatory disorder, and RA patients usually take immunosuppressive agents. Because of the impairment of the immune system and the iatrogenic effect of corticosteroids and immunosuppressive medicine, these patients may be at high risk for severe infections.

3- This study is one of the few to focus on RA patients during the COVID-19 pandemic in Egypt

4- This study found that COVID-19 infection is accompanied by significant worsening of symptoms in RA patients with higher admission rates. More research into expanding cases is required.

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