RESEARCH ARTICLE

# Effects of Biologic Therapies on the Chance of COVID-19 Infection Among Rheumatoid Arthritis and Lupus Patients During the First Wave of the Pandemic

Maryam Sahebari, MD[1]; Zahra Mirfeizi, MD[1]; Kamila Hashemzadeh, MD[1]; Ensie Salavati Nik, Medical Student[2]; Negar Gholampoor Shamkani, Medical Student[2]

*Research performed at the Rheumatic Diseases Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*

*Received: 31 August 2021* *Accepted: 07 April 2022*

## Abstract

**Background:** Patients with rheumatic diseases taking immunosuppressive medications might be at an increased risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Despite the effectiveness of using combined conventional and biological disease-modifying anti-rheumatic drugs(bDMARDs) in managing rheumatic diseases, there have been concerns that taking biological agents may have an additive effect on getting infected with COVID-19. This study evaluates the impact of taking biological agents on altering the chance of getting infected with SARS-CoV-2 in rheumatoid and lupus patients compared to traditional DMARDs.

**Methods:** We carried out a cross-sectional survey study from February 2020 to January 2021 on patients diagnosed with lupus and rheumatoid arthritis disease. COVID-19 infection was confirmed by the presence of symptoms and signs of the disease and para-clinical findings such as lymphopenia and elevated C-reactive protein (CRP) and positive chest CT scan or polymerase chain reaction (PCR) of COVID-19.

**Results:** Out of 591 patients included in this study, 422 (71.4%) had rheumatoid arthritis (RA), and 169 (28.6%) had systemic lupus erythematosus (SLE). Among them, 56 (9.5%) cases were diagnosed with COVID-19 infection. No association was found between age, gender, or type of rheumatological diseases and SARS-CoV-2. There was a significant association between COVID-19 infection and treatment with biological drugs (*P-value<0.05*) regardless of the type of rheumatologic disease. Interestingly, the analysis revealed that the type of biologic drug also altered the chance of COVID-19 infection; In fact, patients who took TNF inhibitors were significantly at a higher risk of disease than those taking Rituximab (*P-value=0.000*). Identical results were observed among RA patients (*P-value<0.001*), however, all 5 (3%) lupus cases treated with Rituximab infected with covid 19.

**Conclusion:** This study develops a better understanding of the risk of immunosuppressive medications for SARS-CoV-2 infection. Patients treated with conventional and biological medicine had a higher disease risk than those taking exclusively conventional drugs. However, more studies are required to deliberate the relation of the reviewed factors with the severity of COVID-19.

**Level of evidence:** II

**Keywords:** Adalimumab, Altebrel, Biological DMARDs, CinnoRA, COVID-19, Etanerecept, Infliximab, Rituximab, Rheumatoid arthritis (RA), Systemic lupus erythematous (SLE)

## Introduction

Coronavirus disease (COVID-19) pandemic has become a significant concern worldwide.[1-3] Intrinsic disturbance of the immune system together with the immunosuppressive effects of prescribed drugs puts people with rheumatic diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) at

***Corresponding Author:*** Zahra Mirfeiz, Rheumatic Diseases Research Center, Mashhad University of Medical Sciences, Mashhad, Iran. Email: mirfeiziz@mums.ac.ir

greater risk of getting different infections.[3] However, whether these patients are at a heightened risk of SARS-CoV-2 disease or more intense COVID-19 outcomes is yet to be determined. Through using data from the new OpenSAFELY electronic platform, Williamson et al. found out that the probability of dying from COVID-19 is slightly higher in people diagnosed with RA, SLE, or psoriasis compared to those without one of the mentioned diagnoses; however, there exists no evidence that patients with rheumatologic conditions have a drastically increased risk than other comorbidities.[4] Besides, since the pandemic, the potential roles of drugs commonly used in rheumatic diseases have been studied comprehensively.[5,6] It is plausible that the COVID-19 pandemic is altering the treatment strategy for disorders like RA or SLE. According to a study published in 2020, rheumatologists were asked to report how the pandemic affected their decision-making regarding the management of patients with rheumatic diseases. The results revealed that treatment decisions were frequently postponed (34%). The majority (74%) of respondents stated that it was less likely to start a biological disease-modifying anti-rheumatic drug (DMARD)/ targeted synthetic DMARD during the pandemic, mainly because of patients' fear of the limited availability of screening procedures and decreased the availability of rheumatological services.[7] Researchers wondered if continuing immune therapies among rheumatic patients is a reasonable choice as these patients have an elevated chance of getting infected. As reported by the NHS, any biologic therapy puts a patient in the high-risk category for acquiring COVID-19.[8] Nonetheless, the findings seem to be controversial. For instance, data from a preliminary survey carried out in Italy do not support the idea that patients given conventional synthetic Disease-modifying anti-rheumatic drugs (csDMARDs), biological DMARDs (bDMARDs), or targeted synthetic DMARDs (tsDMARDs) are more likely to experience respiratory or life-threatening complications from COVID-19 as against the general population.[9] There is evidence that certain immunosuppressive medications can even be beneficial in reducing the odds of hospitalization as a result of COVID-19 infection.[10] In this context, we undertook a cross-sectional study to evaluate the impact of taking biological agents on altering the chance of getting infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in lupus and RA patients compared to traditional DMARDs.

## Materials and Methods

The present study was a cross-sectional, random survey conducted for approximately 11 months, from February 2020 to January 2021, in the period of the first and second, covid 19 peaks in Iran. The participants were adult patients previously diagnosed with RA or SLE by a rheumatologist. Exclusion criteria were non-adherence to medications during the pandemic; patients hospitalized or admitted to ICU for rheumatic disease activity and severity were excluded. A physician interviewed the patients in person, and verbal consent was obtained. Data collected from patients were then entered into a survey and merged into different categories, as demonstrated in and the result section [Table 1]. Diagnosis of COVID -19 at the time of

**Table 1. Demographic and clinical characteristics of the study population**

| | Total n=591 | COVID-19 cases n=56 | Cases without Covid-19 n=535 | *P-value* |
|---|---|---|---|---|
| Female | 526(89.00%) | 53(94.64%) | 473(88.41%) | 0.16 |
| Age(years) | 49.0 ± 11.70 | 49.79 ± 15.58 | 48.92±14.61 | 0.67 |
| Duration of The RA and SLE diseases (years) | 5.7 ± 4.9 | 7.36 ± 4.72 | 5.53±4.88 | 0.008 |
| RA/SLE COVID-19 infection Ratio | 422/169 | 43/13 | 379/156 | 0.34 |
| Treatments(RA + SLE) | | | | |
| Conventional drugs**<br>Conventional drugs**+ b-DMARDs** | 591<br>94 | 56<br>15 | 535<br>79 | 0.019 |
| Conventional drugs**+ anti-TNFs**<br>Conventional drugs**+ Rituximab | 25<br>69 | 10<br>5 | 15<br>64 | <0.001 |
| Disease type | | | | |
| RA | 422(71.40%) | 43(76.78%) | 379(70.84%) | |
| Female | 369(87.44%) | 41(95.34%) | 328(86.54%) | 0.11 |
| Age | 53.66±13.39 | 52.65 ± 15.50 | 53.78±13.75 | 0.15 |
| Duration of the disease(years) | 5.68±4.96 | 7.34 ± 4.62 | 5.49±4.96 | 0.99 |
| Treatment | | | | |
| Conventional drugs**+b-DMARDs** | 89 | 10 | 79 | 0.71 |
| Conventional drugs+ Rituximab(Zytax)<br>Conventional drugs**+ anti-TNFs** | 64<br>25 | 0<br>10 | 64<br>15 | <0.001 |

**Table 1. Continued**

| | | | | |
|---|---|---|---|---|
| SLE | 169(28.59%) | 13(23.21%) | 156(29.15%) | |
| Female | 156(92.30%) | 12(92.30%) | 144(92.30%) | 0.66 |
| Age | 37.37±10.88 | 40.31 ± 12.01 | 37.12±10.78 | 0.74 |
| Duration of the disease(years) | 5.76±4.74 | 7.34 ± 4.62 | 5.62±4.69 | 0.32 |
| Treatment | | | | |
| Conventional drugs +Rituximab (Zytax) | 5 | 5 | 0 | <0.001 |
| Cyclophosphamide (as the most toxic cytotoxic) | 7 | 0 | 7 | 0.10 |

*information about co-existing comorbidities were only available for COVID-19 cases.
**conventional drugs' category includes prednisolone,Azathioprine,Methotrexate, Mycophenolate Mofetil,Cyclophosphamide,Tacrolimus,Cyclospor ine,and Leflunomide for SLE patients and Prednisolone, Azathioprine,Methotrexate, Cyclophosphamide,Tacrolimus,Cyclosporine,and Leflunomide and Sulfasalazine for RA patients.
**b-DMARDs' category includes Rituximab (zytax), for SLE patients and Rituximab (zytax), anti-TNFs including:etanercept (Altebrel),Adalimumab ) Cinnora(,and infliximab for RA patients.
*P-value<0.05* was considered significant.
All the patients were given Hydroxychloroquine as part of their treatments.
; RA, rheumatoid arthritis; SLE, systemic lupus erythematous; b-DMARDs, biologic Disease-Modifying Antirheumatic Drugs.

the study was established by the presence of symptoms and signs of the disease (including presentation of classical clinical manifestations of COVID-19 such as fever, fatigue, and respiratory symptoms) in addition to para-clinical findings suggestive of COVID-19 infection such as lymphopenia and elevated C-reactive protein (CRP) and/ or positive chest X-ray or CT scan or polymerase chain reaction (PCR) of COVID-19. Because this research was conducted at the beginning of the pandemic and there were no approved regional protocols or other accurate clinical diagnosis methods, we used the clinical symptoms and paraclinical factors to detect the COVID-19 patients, including lung x-ray or CTscan, lymphopenia, and CRP.

DMARDs are divided into two subgroups of Conventional DMARDs, including Hydroxychloroquine, Prednisolone, Azathioprine, Methotrexate, Mycophenolate mofetil, Cyclophosphamide, Tacrolimus, Cyclosporine, Leflunomide, and Sulfasalazine and Biologic DMARDs including Rituximab (Zytux), Etanercept (Altebrel), adalimumab (CinnoRA), Infliximab.

Descriptive data was demonstrated as mean ± SD and categorical data as a percentage (fraction). Comparisons between groups were made using Chi-square, Mann-Whitney, and independent sample t-tests. P-value<0.05 was considered statistically significant. All statistical analysis was performed using SPSS V.16.0 software.

## Results

Overall, 591 patients were enrolled in the study, 11% male (n=64). The mean age was 49.0±11.7 years. RA patients comprised the majority of participants (n=422). The mean duration of rheumatic diseases was 5.7±4.9 years. Detailed data on key demographics and clinical manifestations are mentioned in [Table 1].

Among the RA patients, 21.0%(n=89) took biological DMARDs, and 79.0% (n=333) were only taking and cDMARDS. Amid SLE patients, 46.1% (n=78), besides prednisolone/ hydroxychloroquine, took at least one of the below medications: Azathioprine, Methotrexate, Mycophenolate mofetil, Cyclophosphamide, Tacrolimus and Cyclosporine, and Rituximab. Fifty-six of the patients had symptoms of COVID-19 infection, which was confirmed by para-clinic investigations. Forty–three of these cases had RA while the rest (n=13) had SLE. Approximately 95% of the COVID-19 cases were female. The percentages of female cases were 92% and 95% in SLE and RA groups, respectively; however, the analysis did not reveal any association between men and women getting infected with the SARS-CoV 2 [Table 1]. Likewise, the type of rheumatic disease did not correlate with COVID-19 infection(*P=0.349*). Based on the mean age of the cases, no significant correlation was detected between the COVID-19 and non-COVID-19 groups.

The same result was obtained when a comparison was made in each SLE and RA subgroup [Table 1]. Comparing the duration of the rheumatic disorders, the COVID-19 patients had a longer mean disease duration without significant statistical difference. [Details in Table 1]. Considering the type of drugs patients took, taking biological DMARDs was correlated with an increased chance of COVID-19 infection [Table 1].

Furthermore, analysis indicates that the type of biological drug seemed to play an essential role in altering the chance of COVID-19 infection since those taking TNF inhibitors were significantly more likely to get infected than those taking Rituximab (*P<0.001*). The same results were observed regarding RA patients. However, all five lupus cases were treated with Rituximab infected with covid 19. Details on the probable correlation of various medicines with altering the chance of COVID-19 infection are mentioned in [Table 1].

### *Symptoms*

According to our study inclusion criteria, the COVID-19 cases discussed in our manuscript were chosen from those who were neither hospitalized nor admitted to the ICU for rheumatic disease activity and severity. In

fact, regarding the severity of symptoms, all patients suffered from relatively mild-moderate symptoms regardless of the type of medications they were taking. COVID-19 Symptoms were categorized into four groups mentioned as follows: out of 56 COVID-19 patients, 39 cases represented respiratory Symptoms (such as dry cough and shortness of breath), 44 had constitutional signs including fever and shivering, 17 people suffered from GI symptoms (abdominal pain, nausea, vomiting, diarrhea or bloating) and 30 patients reported Myalgia or arthralgia. Among Covid-19 cases who were taking TNF inhibitors, the percentage of respiratory, constitutional, GI, and musculoskeletal symptoms were 25% (N=5), 20% (N=4), 10% (N=2), and 10% (N=2), respectively. Analysis revealed that taking TNF-inhibitors tended to be correlated with respiratory (*P<0.001*), musculoskeletal (*P=0.02*), and GI symptoms (*P<0.001*); however, similar correlation was not found between taking TNF-inhibitor agents and constitutional symptoms (*P=0.32*).

***Comorbidities***

Out of 56 COVID-19 patients, CVD(cardiovascular diseases) was only observed in 12 cases (21.5%), 7 (12.5%) patients had diabetes mellitus, and only two patients (3.6%) represented thyroid diseases and COVID-19 simultaneously. Among all, 6 (1%) were smokers who belonged to the RA group, none of whom were infected with COVID-19.

## Discussion

Disturbance of the immune system and the extensive use of conventional and biologic DMARDs, which is well established in rheumatology practice, has raised concern that rheumatologic patients might be at an increased risk of getting infected with SARS-COV-2. [11]

Our study's results illustrated that taking biological drugs correlates with a higher infection risk than conventional drugs. The outcome contrasts with the previous findings indicating that biological DMARDs do not increase the likelihood of infection. [3,9] The controversy can be due to differences in the studies' populations. Moreover, The studies mentioned above have chosen the cases from hospitalized patients and hence were suffering more severe conditions. In contrast, most of our study cases were only quarantined at home and experienced mild symptoms. Besides, patients taking biological DMARDs might be under careful watch, and thus, clinicians may detect even mild cases. It is worth mentioning that patients in those studies reported having strictly followed the quarantine rules since the beginning of the pandemic, which could also alter the chance of COVID-19 infection. [3] Also, since our study was a cross-sectional study, the association between taking biological DMARDs and COVID-19 infection might be influenced by confounding variables. In the case of RA, our findings were in line with the other studies indicating no significant correlation between COVID-19 infection and the treatment with biological drugs.[12,13] Also, our study findings indicated that the chance of getting infected with SARS-CoV2 was significantly higher among patients taking TNF-inhibitor agents than those taking Rituximab regardless of the preexisting rheumatological disease.

The same results were discovered considering the RA subgroup. These data are in contrast with similar studies.[14,15] It suggests that the type of biological DMARDs may also alter the chance of infection. However, we need to interpret these findings with caution since the overall number of cases taking Rituximab is limited in our study. Besides, Rituximab is given every six months, and It might have been a while ago since our cases received the last dose of Rituximab. Moreover, the results might be influenced by confounding variables. Interestingly, all five lupus cases treated with Rituximab infected with covid 19, it may be proposed that the type of disease in combination with the type of biological DMARDs plays a vital role in covid19 infection; however, we cannot draw any conclusion since these results only show correlation.

Among various factors such as age, gender, and disease duration, the duration of rheumatic disease affected not significantly the chance of SARS-COV-2 infection; this could be attributed to the premature aging of the rheumatologic patients' immune systems that diminishes protection against various organisms.[2]

There are some limitations to our study. Infection with COVID-19 was not confirmed with the PCR test in all the cases since this test was not extensively available at the time of the study in our country. [16,17] Besides, the lack of information on the dosage of the drugs is another limitation of this study. We did not find all the patients due to lockdowns, and some of them may be inpatients or died due to COVID-19. Also, in our study, confounding variables such as the role of multiple medications our cases were taking were not controlled, and, hence, they might have affected our results.

In conclusion, our study findings illustrate a correlation between elevated risk of COVID-19 infection among patients with rheumatologic disorders and using biological DMARDs. More detailed investigations with a larger sample size are needed to broaden our knowledge of the exact effects of various rheumatologic drugs commonly used in treating rheumatic disease and other factors that might increase the likelihood of more severe outcomes in rheumatologic patients.

## Acknowledgments

Mashhad University of Medical Sciences Research Council has appreciated for its cooperation. The article has an ethical code of 981845.

Maryam Sahebari MD[1]
Zahra Mirfeizi MD[1]
Kamila Hashemzadeh MD[1]
Ensie Salavati Nik Medical Student[2]
Negar Gholampoor Shamkani Medical Student[2]
1 Rheumatic Diseases Research Center (RDRC), Mashhad Universality of Medical Sciences, Mashhad, Iran
2 Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

## References

1. Montero F, Martínez-Barrio J, Serrano-Benavente B, et al. Coronavirus disease 2019 (COVID-19) in autoimmune and inflammatory conditions: clinical characteristics of poor outcomes. Rheumatol Int.2020;40(10):1593-8. doi: 10.1007/s00296-020-04676-4
2. Liu Y, Sawalha AH, Lu Q. COVID-19 and autoimmune diseases. Curr Opin Rheumatol. 2021;33(2):155-62. doi: 10.1097/BOR.0000000000000776.
3. Panjavi B, Kamrani RS, Ghane B. The Ups and Downs of COVID-19 Epidemics for Orthopedic Community. Arch Bone Jt Surg. 2020;8(Supplement 1):218-9. doi: 10.22038/abjs.2020.47734.2343.
4. Goldblatt F, Chambers S, Rahman A, Isenberg D. Serious infections in British patients with systemic lupus erythematosus: hospitalisations and mortality. Lupus. 2009;18(8):682-9doi: 10.1177/0961203308101019.
5. Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. Rheumatology. 2012; 52(1):53-61. doi: 10.1093/rheumatology/kes305.
6. Favalli EG, Agape E, Caporali R. Incidence and Clinical Course of COVID-19 in Patients with Connective Tissue Diseases: A Descriptive Observational Analysis. J Rheumatol. 2020;47(8):1296. doi: 10.3899/jrheum.200507.
7. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-6. doi: 10.1038/s41586-020-2521-4.
8. Migkos MP, Kaltsonoudis E, Pelechas E, et al. Use of conventional synthetic and biologic disease-modifying anti-rheumatic drugs in patients with rheumatic diseases contracting COVID-19: a single-center experience. Rheumatol Int. 2021;41(5):903-9. doi: 10.1007/s00296-021-04818-2.
9. Michelena X, Borrell H, López-Corbeto M, et al. Incidence of COVID-19 in a cohort of adult and paediatric patients with rheumatic diseases treated with targeted biologic and synthetic disease-modifying anti-rheumatic drugs. Semin Arthritis Rheum. 2020;50(4):564-70. doi: 10.1016/j.semarthrit.2020.05.001.
10. Dejaco C, Alunno A, Bijlsma JW, et al. Influence of COVID-19 pandemic on decisions for the management of people with inflammatory rheumatic and musculoskeletal diseases: a survey among EULAR countries. Ann Rheum Dis. 2021;80(4):518-26. doi: 10.1136/annrheumdis-2020-218697.
11. Price E, MacPhie E, Kay L, et al. Identifying rheumatic disease patients at high risk and requiring shielding during the COVID-19 pandemic. Clin Med (Lond). 2020;20(3):256-61. doi: 10.7861/clinmed.2020-0149.
12. Quartuccio L, Valent F, Pasut E, Tascini C, De Vita S. Prevalence of COVID-19 among patients with chronic inflammatory rheumatic diseases treated with biologic agents or small molecules: A population-based study in the first two months of COVID-19 outbreak in Italy. Joint Bone Spine. 2020;87(5):439-43. doi: 10.1016/j.jbspin.2020.05.003.
13. Schoot TS, Kerckhoffs APM, Hilbrands LB, van Marum RJ. Immunosuppressive Drugs and COVID-19: A Review. Front Pharmacol. 2020;11: 1333. doi: 10.3389/fphar.2020.01333.
14. Calabrese C. COVID-19 and your rheumatology patients. Cleve Clin J Med. 2020. doi: 10.3949/ccjm.87a.ccc027.
15. Sanchez-Piedra C, Diaz-Torne C, Manero J, et al. Clinical features and outcomes of COVID-19 in patients with rheumatic diseases treated with biological and synthetic targeted therapies. Ann Rheum Dis. 2020;79(7):988-90. doi: 10.1136/annrheumdis-2020-217948.
16. Freites Nuñez DD, Leon L, Mucientes A, et al. Risk factors for hospital admissions related to COVID-19 in patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2020;79(11):1393-9. doi: 10.1136/annrheumdis-2020-217984.
17. Bachiller-Corral J, Boteanu A, Garcia-Villanueva MJ, et al. Risk of Severe COVID-19 Infection in Patients With Inflammatory Rheumatic Diseases. J Rheumatol. 2021;48(7):1098-102. doi: 10.3899/jrheum.200755.
18. Santos CS, Férnandez XC, Moriano Morales C, et al. Biological agents for rheumatic diseases in the outbreak of COVID-19: friend or foe? RMD Open. 2021;7(1):e001439. doi: 10.1136/rmdopen-2020-001439.
19. Mahmoudi S, Mehdizadeh M, Shervin Badv R, et al. The Coronavirus Disease 2019 (COVID-19) in Children: A Study in an Iranian Children's Referral Hospital. Infect Drug Resist. 2020;13:2649-55. doi: 10.2147/IDR.S259064.
20. Salehi-Abari I, Khazaeli S, Salehi-Abari F, Salehi-Abari A. Practical Guideline for Screening the Patients with SARS-CoV-2 Infection and Persian Gulf Criteria for Diagnosis of COVID-19. Advances in Infectious Diseases. 2020;10(03):67. DOI:10.4236/aid.2020.103008