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Original Article

Comparison of Respiratory Complications of COVID-19 among Patients with Rheumatological Conditions Taking Biological Disease-Modifying Anti-Rheumatic Drugs and Conventional Synthetic Disease-Modifying Antirheumatic Drugs

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ABSTRACT

Objective: To compare the respiratory complications of COVID-19 among patients with rheumatological conditions taking bDMARDs and csDMARDs at Pak Emirates Military Hospital Rawalpindi.

Study Design: Comparative prospective study.

Place and Duration of Study: Pak Emirates Military Hospital, Rawalpindi Pakistan from Mar to May 2020.

Methodology: Patients diagnosed with COVID-19 on polymerase chain reaction having previously rheumatological conditions managed either with bDMARD or cs DMARD were included in the study. They were followed up for three weeks after the positive polymerase chain reaction. Complications leading to the use of oxygen or ICU support or death were compared in both groups of patients.

Results: A total of 82 patients with any rheumatological condition managed either with bDMARD or csDMARD tested positive for covid-19 on polymerase chain reaction and were included in the final analysis. 30 (36.6%) patients were taking bDMARDs while 52 (63.4%) were taking csDMARD. In addition, 4 (4.8%) low dose oxygen therapy, 5 (6.1%) required moderate dose oxygen therapy, while 5 (6.1%) required severe dose oxygen therapy or intensive care unit support. 2 (2.4%) patients died within the three weeks. The requirement of moderate or severe dose oxygen and intensive care unit support was found statistically significantly more in the group taking csDMARDS.

Conclusion: The presence of complications of COVID -19 and the requirement of oxygen and intensive care unit support were present in some of the patients taking DMARDs. Among the DMARDs, bDMARDs were less linked with complications, but large studies with better design required better results.

Keywords: COVID-19, Complications, DMARDs.

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INTRODUCTION

Humans have fought wars against not only humans but various infectious pandemics which threatened the existence of mankind in this universe.[1] This time in 2019, it was COVID -19, and its origin was one of the most populous countries of the world, China.[2] It started from there, and then within weeks and months, all parts of the world were affected, and health organizations and health professionals all were in thick soup to bear the burden of this unexpected challenge threatening the lives of millions of people around the globe.

All the countries have been trying their level best according to the resources they have and the maturity of their respective health systems.[3] Outpatients departments for routine medical conditions have not been working to their full since the beginning of this pandemic, making prone to chronic patients with already compromised immunity to acquire this infection.[4,5] Chronic medical conditions especially immune-related disorders may compromise the immunity of individual and may prone him towards complicated disease spectrum of COVID-19,[5] but on the other hand, the immunomodulator medications they are taking may have a protective role in managing the immune storm generated by the covid-19 virus in human body.[6]

Rheumatology medications may have a role in modulating the immune response, so they have been tried and tested in fighting the battle against this novel virus. Monti *et al*. after their little research on rheumatology patients taking the bDMARDs, concluded that patients with chronic arthritis treated with bDMARDs or tsDMARDs do not seem to be at increased risk of respiratory or life-threatening complications from SARS-CoV-2 compared with the general population.[7] Fernandez-Gutierrez *et al.* in their study to look for the role of the disease-modifying agent in predicting COVID-19 response in rheumatological patients, con-

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cluded that age, gender and type of rheumatological disorder have a statistically significant relationship with response to Covid-19 infection but types of DMARDs used had no such relationship.[8] Gupta *et al*. conducted a survey among members of Indian academy of rheumatology and summarized their responses as that most rheumatologists recommend changes in the ongoing treatment of rheumatological condition after acquiring COVID-19 and discontinuation of bDMARDs for a better response among the patients suffering from rheumatological disorders and COVID-19.[9]

At present, clinicians have been struggling to find the best management plan for patients of COVID-19 in the general population and with comorbidities. For patients with rheumatological conditions, Favalli *et al*. published a comprehensive paper. They concluded that bDMARDs, especially IL-6 inhibitors such as Tocilizumab or Sarilumab, might be more suitable for managing most critical cases of interstitial pneumonia complicated by cytokine release syndrome. However, the results are still preliminary and need more research.[10] We therefore, planned this study to compare respiratory complications of COVID-19 among patients with rheumatological conditions taking bDMARDs and csDMARDs at our tertiary care hospital.

METHODOLOGY

This comparative prospective study was conducted at Pak Emirates Military Hospital, Rawalpindi Pakistan between March and May 2020. Ethical approval was taken from the Ethical Committee of the hospital via letter no A/124-E 121. The sample size was calculated using the WHO calculator with the population prevalence proportion of complications of DMARDs 3%.[11] Non probability consecutive sampling was used to gather the sample.

Inclusion Criteria: All the COVID-19 PCR-positive patients between 18 and 70 years, diagnosed with any immune-mediated inflammatory rheumatic diseases by consultant rheumatologist and managed with bDMARDs or csDMARDs in adequate doses according to the guidelines set by the American College of Rheumatology,[12] were included in the study.

Exclusion Criteria: Patients with any comorbid systemic illness other than immune-mediated inflammatory rheumatic diseases were made part of the exclusion criteria. Pregnant females were also not included in the study. Patients with solid or haematological malignancy were also excluded from the study. Patients whose follow-up was not possible for three weeks were also part of the exclusion criteria. Patients receiving bDMARD or csDMARD for any other disease other than rheumatological disorder were also not included.

Patients suspected of COVID -19, which turned out to be positive on PCR test,[13] having diagnosis of any immune-mediated inflammatory rheumatic diseases managed with bDMARDs or csDMARDs, were included in the study after the application of inclusion /exclusion criteria. They were followed up for three weeks for the presence of any respiratory complications. Routine blood tests, chest x-ray and CT scans were done for all the patients. Findings on chest X-ray and CT scans were not made part of the study, and only clinical complications of the respiratory system managed with a mild, moderate or severe dose of oxygen or ICU support were studied and compared in both groups. Mild oxygen dose was defined as up to 3 litres/min, moderate as 4 to 10 litres/min, and severe as >10 litres/min. No changes in dosing of bDMARDs or csDMARDs were made in any of the study participants during illness except if the critical care team suggested any change after shifting to ICU.

Statistical Package for Social Sciences (SPSS) version 24.0 was used for the data analysis. Frequency and percentage were calculated for the qualitative variables like gender and presence of each complication, whereas mean and standard deviation was calculated for the quantitative variables like age of the patients included in the study. The chi-square test was used to compare the respiratory complications of COVID-19 among patients with rheumatological conditions taking bDMARDs and csDMARDs. The *p*-value less than or equal to 0.05 was considered significant.

RESULTS

Around 90 patients with various rheumatological disorders found COVID-19 positive on PCR and approached for the study, but after application of inclusion /exclusion criteria, 82 were included in the study and monitored for any complications. Of these 82 patients, 30 (36.6%) were male, while 52 (63.4%) were female. Table-I showed the demographic characteristics of patients. The most common immune-based condition among patients included in the study was rheumatoid arthritis 36 (43.9%), followed by psoriatic arthritis 18 (21.9%). Out of 82 study participants, 30 (36.6%) were taking b DMARDs while 52 (63.4%) were taking csDMARD. A total of 4 (4.8%) patients required low dose oxygen therapy, 5 (6.1%) required moderate dose oxygen therapy, while 5 (6.1%) required severe dose oxygen therapy or ICU support. 2 (2.4%) patients died

within the three weeks. Table-II showed that the requirement for moderate or severe dose oxygen and ICU support was statistically significantly higher in the group taking csDMARDS (*p*-value<0.05).

Table-I: Characteristics of Study Participants (n=82)

Characteristics	n (%)
Age (years)	
Mean ± SD	45.19±3.45
Range (min-max)	20 - 63
Gender	
Male	30 (36.6)
Female	52 (63.4)
Underlying Immune Based Condition	
Rheumatoid arthritis	36 (43.9)
Psoriatic arthritis	18 (21.9)
Psoriasis	12 (14.6)
Ankylosing spondylitis	10 (12.2)
Others	6 (7.3)
Respiratory Complications	
Requirement of low dose oxygen	4 (4.8)
Requirement of moderate dose oxygen	5 (6.1)
Requirement of severe dose oxygen or	5 (6.1)
Intensive care unit shifting death	2 (2.4)

Table-I: Comparison of Various Variables among Patients taking bDMARDs and cs DMARDs (n=82)

Factors Studied	Patients Taking bDMARDs (n= 30) n(%)	Patients Taking csDMARDs (n=52) n(%)	*p*-value
Low Dose Oxygen			
No	28 (93.3)	50 (96.2)	0.575
Yes	02 (6.7)	02 (3.8)	
Medium Dose Oxygen			
No	30 (100)	47 (90.4)	0.029
Yes	0 (0)	05 (9.6)	
Severe Dose Oxygen or Intensive Care Unit Requirement			
No	30 (100)	47 (90.4)	0.029
Yes	0(0)	5 (9.6)	
Death			
No	29 (96.7)	51 (98.1)	0.695
Yes	1 (3.3)	1 (1.9)	

DISCUSSION

Pakistan has been facing the pandemic in full blow in the past few weeks, and the number of new cases and death have been on arise constantly.[14,15] Being a developing country, the healthcare system of Pakistan has limited capacity to absorb the shock and the healthcare services already getting choked with the patients.[15] Immune-mediated disorders have to be constantly monitored by the treating physicians as they may flare anytime or the medications may cause serious adverse effects. During this pandemic, there has been a debate regarding the use of immunomodulatory medications to counter the cytokine storm seen in complicated COVID-19 patients.[4,5] We have a busy rheumatology department catering to a large number of patients; therefore, we planned this study to compare the respiratory complications of COVID-19 among patients with rheumatological conditions taking bDMARDs and csDMARDs at Pak Emirates Military Hospital Rawalpindi.

Haberman *et al*. published a case series rewarding a course of COVID-19 among patients with immune-based inflammatory disorders. They concluded that the percentage of patients receiving bDMARDs or JAK inhibitors had fewer chances of getting complications and admission to the hospital. The overall incidence of hospitalization among patients who had received these medications on a long-term basis was 11% (7 of 62 patients).[16] Our conclusion was quite similar as patients on bDAMRDs had statistically significantly less chance of needing a moderate or severe dose of oxygen re ICU admission for respiratory complications than patients taking csDMARDs.

Javed *et al*. published an interesting paper in this regard, summarizing that data from China suggest using immunomodulatory therapies like Chloroquine, Tocilizumab (preferred right now because of the track record), and Baricitinib can quench the cytokine storm that ensues in patients with very severe COVID-19 pneumonia. Patients admitted for severe COVID-19 infections should probably hold maintenance therapies; these decisions are best left to the rheumatology/ infectious disease teams taking care of them. Rheumatologists and infectious disease specialists should be working together in this epidemic as clear data are unavailable, thus making recommendations speculative.[15] As very little is known about this novel virus's course and management. Therefore, multidisciplinary approach may be adopted, and decisions should be made according to the presentation in each case.

Gianfrancesco *et al.* studied characteristics of COVID-19 patients suffering from rheumatic diseases. They concluded that tumour necrosis factor inhibitor (anti-TNF) use was associated with a reduced odds of hospitalization (OR 0.40, 95% CI 0.19 to 0.81). In contrast, no association with antimalarial use (OR 0.94, 95% CI 0.57 to 1.57) was observed.[17] We did not study individual drugs or sub-groups of medications, but TNF inhibitors represent the bDMARDS which were less associated with respiratory complications in our study.

We have not been using JAK inhibitors in our set-up as they have not been available yet, but they have been one of the new bDMARDS. In addition, Seif *et al*. studied regarding the potential role of JAK inhibitors in fighting cytokine response generated by COVID-19 in complicated cases. They concluded that a combination of Methotrexate and Baricitinib (JAK inhibitors) has led to outstanding clinical outcomes in managing immune-mediated storm in rheumatological conditions; therefore, the addition of Baricitinib to Methotrexate might be a potential strategy.[18] Though JAK inhibitors are not available in our set-up, the superiority of bDMARDs in our study and the recommendation of Seif *et al*. may be considered in devising management plans for COVID-19 patients.

Xu *et al*. studied the role of one of the bDMARDs. They concluded that preliminary data show that Tocilizumab had a clear role in improving the clinical condition of patients with complications of COVID-19.[19] Our patients who were using any of the bDMARDs also had fewer chances of respiratory complications. In addition, their recovery course was better than those taking csDMARDs.

LIMITATIONS OF STUDY

We did not follow up with patients for a long time to record the long-term prognosis, so results could only reflect a short-term clinical course. In addition, there was a variety of medications in both groups, so broadly studying bDMARDs and cDMARDS would not help us identify the exact medication options that may be more useful for COVID-19-related cytokine response as this virus is novel, so more studies are required to find the suitable options for these patients.

CONCLUSION

The presence of complications of COVID-19 and the requirement of oxygen and intensive care unit support were present in some of the patients taking DMARDs. Among the DMARDs, bDMARDs were less linked with complications, but large studies with better design required better results.

Conflict of interest: None.

Author's Contribution

AAC: Study design, data collection, AF: Data collection, MSK: Study design and data interpretation, SS: Data interpretation, SNA:, MZH: Data design.

REFERENCES

1. Huremović D. Brief History of Pandemics (Pandemics Throughout History). Psychiatr Pandemics 2019; 1(1): 7-35.
2. Ge H, Wang X, Yuan X. The epidemiology and clinical information about COVID-19. Eur J Clin Microbiol Infect Dis 2020; 39(6): 1011-1019. doi: 10.1007/s10096-020-03874-z.
3. Stevens MP, Doll M, Pryor R, Godbout E, Cooper K, Bearman G. Impact of COVID-19 on traditional healthcare-associated infection prevention efforts [published online ahead of print, 2020 Apr 16]. Infect Control Hosp Epidemiol 2020; 1(1): 1-2. doi: 10.1017/ice.2020.141.
4. Hopkins TJ, Erika H, Mark Z, Priyanka P, Paul S. Covid-19: how doctors and healthcare systems are tackling coronavirus worldwide BMJ 2020; 368(1):m1090. doi: 10.1136/ bmj.m1090.
5. Garg S, Kim L, Whitaker M, O'Hallloran A, Cummings C. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019-COVID-NET, 14 States, March 1–30, 2020. Morb Mortal Wkly Rep 2020; 69(15): 458–464. doi: 10.15585/mmwr.mm6915e3.
6. Schulze-Koops H, Specker C, Iking-Konert C, Holle J, Moosig F, Krueger K. Preliminary recommendations of the German Society of Rheumatology (DGRh eV) for the management of patients with inflammatory rheumatic diseases during the SARS-CoV-2/COVID-19 pandemic. Ann Rheum Dis 2020; 79(6): 840-842. doi: 10.1136/annrheumdis-2020-217628
7. Monti S, Balduzzi S, Delvino P, Bellis E, Quadrelli VS, Montecucco C. Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. Ann Rheum Dis 2020; 79(5): 667-668. doi: 10.1136/ annrheumdis-2020-217424.
8. Fernandez-Gutierrez B, Leon L, Madrid A, Rodriguez-Rodriguez L, Freites D. Hospital admissions in inflammatory rheumatic diseases during the COVID-19 pandemic: incidence and role of disease modifying agents. medRxiv 2020; 05(21): 20108696.
9. Gupta L, Misra D. Management of rheumatic diseases in the times of COVID-19 pandemic-perspectives of rheumatology practitioners from India. Med Rxiv 2020; 4(3): 20048389.
10. Favalli EG, Ingegnoli F, De Lucia O, Cincinelli G. COVID-19 infection and rheumatoid arthritis: Fara-way, so close!. Autoimmun Rev 2020; 19(5): 102523. doi: 10.1016/ j.autrev.2020.102523.
11. Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G. Real estimates of mortality following COVID-19 infection Lancet Infect Dis 2020; 20(7): 773. doi: 10.1016/S1473-3099(20)30195-X.
12. American College of Rheumatology. A message from the ACR about coronavirus disease 2019 (COVID-19), 2020. [internet] available at: https://www.rheumatology.org/announcements.
13. Zhai P, Ding Y, Wu X, Long J, Zhong Y, Li Y. The epidemiology, diagnosis and treatment of COVID-19. Int J Antimicrob Agents 2020;55(5):105955. doi: 10.1016/j.ijantimicag.2020.105955.
14. Waris A, Atta UK, Ali M, Asmat A, Baset A. COVID-19 outbreak: current scenario of Pakistan. New Microbes New Infect 2020;35(3):100681. doi: 10.1016/j.nmni.2020.100681.
15. Javed B, Sarwer A, Soto EB, Mashwani ZU. Is Pakistan on track to have COVID-19 transmission and mortality rates similar to those of Italy, Iran or the USA? [published online ahead of print, 2020 Apr 15]. Drugs Ther Perspect 2020; 36(7): 293-297.doi: 10.1007/s40267-020-00726-w
16. Haberman R, Axelrad J, Chen A, Castillo R, Yan D, Izmirly P, et al. Covid-19 in immune-mediated inflammatory diseases — case series from New York. N Engl J Med 2020; 383(3): 85-88. doi: 10.1056/NEJMc2009567.
17. Gianfrancesco M, Hyrich KL, Al-Adely S. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2020; 79(4): 859-866. doi: 10.1136/annrheumdis-2020-217871.
18. Seif F, Aazami H, Khoshmirsafa M, Kamali M, Mohsenzadegan M, Pornour M et al. JAK Inhibition as a New Treatment Strategy for Patients with COVID-19. Int Arch Allergy Immunol 2020;181(6):467-475. doi: 10.1159/000508247.
19. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci USA 2020; 117(20): 10970-10975.