COVID-19 Pandemic in Women–Rheumatologist's Perspective

Benzeeta Pinto[1] Rashmi Roongta[2]

[1]Department of Clinical Immunology and Rheumatology, John's Medical College, Bengaluru, India
[2]Department of Rheumatology, Institute of Post Graduate Medical Education and Research, Kolkata, India

Address for correspondence Benzeeta Pinto, DM, Department of Clinical Immunology and Rheumatology, John's Medical College, Bengaluru, India (e-mail: benzeeta@gmail.com).

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Abstract

COVID-19 has caused unprecedented challenges to every field. Rheumatic diseases (RD) are more common in women compared with men. Patients with RD are predisposed to infections both because of their disease and immunosuppressive medication. The severity of COVID-19 in women is less as compared with men among the general population. It is not known if the risk is higher in women with RD compared with other women. Currently, published data of COVID-19 in RD suggests similar or mildly increased risk in patients with RD but sex disaggregated data is not available. In this article, we review the current evidence of COVID-19 in RD with an emphasis on women.

Keywords
- COVID 19 in women
- rheumatic diseases
- immunosuppressants

Introduction

Coronavirus disease 2019 (COVID-19) is the third documented zoonotic spill over to humans in just two decades, which has spread rapidly across the globe, infecting more than 13 million people and resulting in 5 lakh deaths over a short span of 8 months. The WHO declared SARS-CoV-2 as a global pandemic in March 2020.[1] As of June 27, 2020, India has crossed the 5 lakh mark for COVID-19 cases, making India the fourth highest affected country.[2] COVID-19 has led to significant changes in clinical practice and several questions remain unanswered. COVID-19 is of relevance to the rheumatologist for many reasons. First and foremost, patients with rheumatic diseases (RD) on immunomodulators are at an increased risk of infections. Second, the pathogenesis of COVID-19, especially severe disease which is associated with immune dysregulation, has many similarities to macrophage activation in RD. Antirheumatic drugs like steroids, hydroxychloroquine, and tocilizumab are being repurposed to tackle the disease.

COVID-19 and Women

Very early in the pandemic, it was evident that men were more severely affected by COVID-19 compared with women. Sex disaggregated data wherever available indicate similar attack rates for men and women; however, severity in the form of ICU admissions and mortality are higher in men even after adjusting for age.[3,4] The reasons are not absolutely clear. The role of female hormones and immunological differences may contribute but are not clearly elucidated. In general, estrogen promotes immune responses and testosterone suppresses it. These differences are also responsible for higher prevalence of autoimmune diseases in women. Women have better antibody responses to vaccines as compared with men.[5] SARS-Cov-2 enters the cells by binding to the angiotensin-converting enzyme 2 (ACE-2) receptors. ACE-2 is a membrane-bound protein which is ubiquitous and expressed in multiple tissues, including lungs, vasculature, heart, adipose tissue, gut, kidneys and central nervous system (CNS). After binding, a serine protease TMPRSS2 facilitates viral entry. Both these proteins may be regulated by sex hormones. Estrogen downregulates ACE-2 receptors. Transcription of TMPRSS2 is regulated by androgenic ligands and an androgen receptor binding element in the promoter.[4] Women are also found to have increased expression of toll-like receptor 7 (TLR7) gene which is located on the X chromosome. TLR7 is a pattern recognition receptor for RNA viruses and women thereby have a higher interferon 1 response and lower IL-6 production in response to viral infections.[5] The differences in severity may also be due to gender-related risk factors such as higher

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incidence of comorbidities and smoking in males compared with females. Differences in hand washing and social isolation may also contribute.[4,6]

Cytokine Storm in COVID-19

The immunopathogenesis of SARS-CoV-2 is complex and still being understood. The reason few patients go on to develop a severe illness, while few are asymptomatic or just have a mild illness is a puzzle yet to be solved. Severe illness of HCoV infections is associated with increased cytokine and chemokine levels, which is similar to hemophagocytic lymphohistiocytosis (HLH). Macrophage activation syndrome (MAS) is a form of secondary HLH seen in RD. The common features include lymphocytopenia, elevated CRP, IL-6, hyperferritinemia, and coagulopathy similar to that seen in MAS and HLH. However, the cytokine response in COVID-19 is lung-centric and lacks the organomegaly and cytopenia seen in classical HLH and MAS associated with RD.[7] Cytokine storm in COVID-19 seems to be triggered by immune evasion by the virus. High-viral loads, certain human leukocyte antigen (HLA) haplotypes and immunodeficiency (due to age or comorbidities) may contribute to reduced antiviral responses. In addition, the virus itself may interfere with type 1 interferon response, which is required for viral clearance.[8] This, in turn, leads to excessive type 2 interferon response and activation of monocyte/macrophages and consequent cytokine release syndrome (CRS).[9]

COVID-19 in Rheumatic Diseases (RD)

It is well-established that patients with RD are at an increased risk of infections. This risk may be due to the disease itself such as in systemic lupus erythematosus (SLE) or due to the treatment. There is little data on COVID-19 in patients with RD. The incidence of COVID-19 in RD was found to be similar to the general population in the same region in two studies from Italy.[10,11] Patient with RD exerted due diligence when it came to preventive measures. This could also contribute to the low incidence in this population.[10] A study from Spain reported a 1.32-fold higher risk of PCR positive COVID-19 requiring hospital admission in chronic inflammatory diseases compared with general population. The risk was however variable, depending on the disease and treatment. Patients with inflammatory arthritis on targeted synthetic or biologic disease-modifying drugs had higher risk than patients on conventional synthetic drugs. The risk was similar to general population in patients with SLE and was higher in other systemic autoimmune diseases.[12] The severity of COVID-19 in RD seems to be similar to the general population.[10] A global rheumatology alliance that included 600 patients (70% female) of RD from multiple centers found a mortality of 9% in a patients with RD and COVID-19. The most common RD was rheumatoid arthritis (RA). Age above 65 years, cardiovascular comorbidity, diabetes, chronic lung disease (CLD), and chronic kidney disease (CKD) were associated with higher odds for hospitalization. Female sex was not associated with lower risk of hospitalization. Interestingly, the use of tumor necrosis factor (TNF) inhibitors was associated with lower odds of hospitalization, while there was no association with use of nonsteroidal anti-inflammatory drugs (NSAIDs) or antimalarials.[13] A study from China also reported higher respiratory failure in patients with RD as compared with patients without RD.[14] This study included 21 patients with RD and COVID-19 and had a higher proportion of females (81% vs. 50% RD versus non RD, p 0.009). A study from US of 52 patients with RD and COVID-19 also noted higher need for mechanical ventilation in RD compared with non-RD, however mortality was similar. The sex ratio in this study of RD with COVID-19 was similar to non-RD patients.[15] However, most of these data is predominantly from hospital-based studies that may have missed mild cases. This variable risk may also be associated with the distribution of other risk factors such as diabetes mellitus and not RD as such. Additionally, rheumatic diseases are more common in women than in men and since COVID-19 is more severe in men, this may also influence the severity of COVID-19 in RD. Sex disaggregated data will be required to understand if women with RD are at a higher risk compared with women without RD.

Clinical Features of COVID-19 in Rheumatic Diseases (RD)

The clinical presentation of COVID-19 ranges from asymptomatic to severe pneumonia. Asymptomatic patients may account for 40 to 45% of the patients. However, patients without symptoms may have objective evidence of illness in the form of ground glass opacities (GGOs) on CT chest.[16] Symptomatic infections vary in severity from mild to critical requiring mechanical ventilation. The most common presenting symptoms include fever and cough; sputum production, sore throat, fatigue and diarrhea are other common symptoms.[17] In a report from Chinese centre for disease control and prevention that included 44,500 cases, 81% were reported as mild. Severe disease was seen in 14% and critical disease in 5%. The overall case fatality rate was 2.3%, however increased mortality was noted in patients with cardiovascular disease, diabetes, chronic respiratory disease, hypertension and cancer.[18] Severe COVID-19 is associated with CRS. Elevated ferritin which is a feature of HLH is a predictor of mortality in COVID-19. Reduced lymphocyte counts and thrombocytopenia are other markers of severity in COVID-19.[19] The most common radiological feature is bilateral GGO in CT chest. Pleural effusion and cavitation are uncommon.[20] Thrombotic manifestations both venous (deep venous thrombosis and pulmonary embolism) and arterial (stroke, myocardial infarction) are also reported in COVID-19. Most of the patients with thrombosis had traditional risk factors.[21] Antiphospholipid antibodies have been described in three patients with COVID-19 along with thrombosis.[22]

The clinical features of COVID-19 in RD are similar to general population. Fever, fatigue and diarrhea were the most common symptoms in a series of patients with RD and COVID-19. GGOs were the most common finding on CT chest, while pleural effusion, which is otherwise uncommon in

COVID-19, was seen in 2 of 21 patients. Four patients had a flare of RD during COVID-19.[14] Two series reported a higher need for ventilatory support in patients with RD.[14,15] Clinical features of COVID-19 such as fever, arthralgias, myalgias, cytopenia, myocarditis and elevated ferritin may mimic flare of rheumatic diseases. Fever may not always be present in patients who are immunocompromised and hence high index of suspicion is necessary.[23] An atypical Kawasaki-like disease has been described in pediatric patients with COVID-19. In a series from France, 10 out of 16 patients fulfilled the American Heart Association definition for Kawasaki disease (KD). Most (94%) had mucocutaneous manifestations and seven (44%) had myocarditis. As compared with patients with classical KD, patient with KD triggered by COVID-19 were older and had a higher incidence of myocarditis.[24]

Immunomodulatory Treatment in COVID-19

Several immunomodulatory drugs are being tried in COVID-19 (►**Table 1**). The antimalarials chloroquine and hydroxychloroquine were one of the first drugs to be tested for the disease. The antiviral efficacy of these drugs is based on increase in the pH of endosomes, interfering with virus fusion and release. Initial in vitro studies and small clinical studies showed efficacy in viral clearance as well as clinical outcomes.[25] Two clinical trials that followed have not shown any benefit of hydroxychloroquine for treatment or for post-exposure prophylaxis. A randomized controlled trial (RCT) from China in 150 patients with COVID-19 (148 with mild/moderate) showed no difference in negative conversion in the hydroxychloroquine group as compared with standard to care.[26] In a study exploring postexposure prophylaxis in 821 patients with moderate to high risk exposure hydroxychloroquine did not prevent illness as compared with control group.[27]

Table 1 Immunomodulatory treatment in COVID-19

Drug	Proposed mechanism of Action	Evidence
Hydroxychloroquine	Antiviral action by increasing pH of endosomes preventing viral fusion and release	RCT for moderate, severe disease showed no benefit[26] RCT showed no benefit in postexposure prophylaxis[27]
Tocilizumab	Blocks IL-6 which plays a central role in ARDS and cytokine release syndrome	Case series showed some benefit[28–30] RCT (COVACTA)–awaited
Anakinra	IL-1 receptor antagonist, mitigates the hyperinflammatory response	Small cohort study showed mortality benefit in severe COVID-19[32]
Steroids	Dampens the hyperinflammatory response	RCT showed mortality benefit in patients requiring oxygen, no benefit in mild COVID-19[33]
Janus Kinase inhibitors	Inhibits clathrin mediated endocytosis thereby preventing viral entry	Pilot study of Baricitinib showed positive results[36] RCTs ongoing
Convalescent plasma therapy	Passive immunity	Single RCT–no clear benefit[37]

Abbreviations: ARDS, acute respiratory distress syndrome; RCT, randomized control trial.

IL6 is significantly elevated in severe COVID-19 and CRS and is a marker for severity. Monoclonal antibodies against IL6, tocilizumab (TCZ) and sarilumab which are approved for use in RA and other RD, have been tried in severe disease. A study from China which used TCZ in 21 COVID-19 patients, 20 of whom were hypoxic, reported improvement in hypoxemia and radiological clearance.[28] In a prospective study of 100 patients with COVID-19 pneumonia and acute respiratory distress syndrome (ARDS) requiring ventilation in China, 77% improved with TCZ.[29] All patients had hyperinflammatory syndrome evidenced by lymphopenia, elevated CRP, ferritin and IL6. A large retrospective study in which 544 patients with severe COVID-19 received either standard care or TCZ therapy showed significant reduction in mortality rate and risk of invasive ventilation in patients treated with the latter.[30] Both TCZ and sarilumab are undergoing trials for COVID-19.[31]

Anakinra, an IL-1 receptor antagonist, was also tested in severe COVID-19 in small retrospective study. IL-1 is elevated in COVID-19 associated CRS and may contribute to the ARDS. This study included 52 consecutive patients in anakinra group and 44 historical controls with severe COVID-19 pneumonia. The need for ICU admission and invasive mechanical ventilation or death was lower in the anakinra group 13 (25%) as compared with controls 32 (73%).[32]

Steroids may be effective in mitigating inflammation in severe disease and CRS. Dexamethasone in the dose of 6 mg/day either orally or parenterally was found to decrease mortality in patients requiring oxygen in a recent RCT. The mortality benefit was found both in patients receiving invasive mechanical ventilation (29.3% vs. 41.4%) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%). There was no benefit found in patients not on any respiratory support at randomization.[33]

Other drugs which may be potentially beneficial based on their mechanism of action are Janus kinase (JAK) inhibitors, which are approved for treatment of RA. These drugs may be effective in CRS.[23] JAK inhibitors like baricitinib and tofacitinib and IL-6 inhibitors such as TCZ have been studied in COVID-19. A study identified a group of drugs which inhibit clathrin-mediated endocytosis by targeting members of numb-associated kinase (NAK) family, including AP-2-associated protein kinase 1 (AAK1) and cyclin G-associated kinase (GAK), which have shown to reduce viral infection in vitro. Baricitinib was identified as a NAK inhibitor with high affinity for AAK1, thus helping in countering COVID-19 infections at doses used to treat RA (2–4 mg daily). Tofacitinib, however, did not show detectable inhibition of AAK1.[34] This theory was contested by Favalli et al, based on

the fact that baricitinib blocks the JAK- signal transducer and activator of transcription (STAT) pathway and this would interfere with the signaling of interferon, which is one of the most powerful innate immune responses to prevent viral replication.[35] A pilot study of use of baricitinib in moderate COVID-19 showed significantly better clinical and laboratory parameters in patients treated with it.[36] Further studies are required to confirm the efficacy of baricitinib in COVID-19. There is currently no data on other drugs approved for RA like upadacitinib or filgotinib and their association with COVID-19.

Convalescent plasma therapy has also been tried in the treatment of COVID-19. It is hypothesized that the pathogen neutralizing antibodies in patients who recover may confer passive immunity to patients with COVID-19. An RCT conducted in 103 patients with severe COVID-19 in China did not find any benefit with convalescent plasma therapy as compared with standard of care. This study was however underpowered to detect a difference.[37] A Cochrane database review that included 20 studies (only one RCT) concluded that plasma therapy was of uncertain benefit.[38]

Recently, itolizumab, an anti-CD6 IgG1 monoclonal antibody used for chronic plaque psoriasis, has been the first biologic to be approved by the Drug Controller General of India to treat CRS in moderate-to-severe COVID-19. However, there is little published data on this drug in COVID-19. The phase 2 trial on which the approval was based is yet to be published.[39]

Treatment of Rheumatic Diseases (RD) during the Pandemic

Patients with RD should be advised usual precautions such as social distancing, hand hygiene, face masks, and avoiding crowded areas. Treatment for life and organ threatening diseases should continue as usual (►**Table 2**). Use of NSAIDs should be restricted and paracetamol should be preferred for pain relief.

Steroids should not be interrupted abruptly in a patient on chronic long-term steroids due to risk of secondary adrenal insufficiency. Most guidelines recommend the use of the lowest dose of steroid which is required to keep the disease activity under control.

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as antimalarials, methotrexate, leflunomide, and sulfasalazine may be continued (►**Table 1**). In a patient with suspected or proven COVID-19, immunomodulators except antimalarials may be withheld.[40] Cyclophosphamide use has been classified in the high-risk group for acquiring COVID-19 by British Society of Rheumatology (BSR).[41]

While ongoing treatment may be continued, decision to start biologic DMARDS or targeted synthetic DMARDS may be individualized (►**Table 1**). ACR guidelines state that patients with RD, in the absence of COVID-19 infection, may continue IL-6 inhibitor therapy if available. Switch to a different biologic should be considered in case of nonavailability. The panel noted uncertainty regarding the use of JAK inhibitors in this situation. In patients with moderate-to-high disease activity despite optimal treatment with csDMARDs, it was suggested that biologics may be started. Following COVID-19 exposure, the panel suggested that immunosuppressants, non-IL-6 biologics, and JAK inhibitors should be stopped temporarily, pending a negative test result for COVID-19 or after 2 weeks of symptom-free observation. IL-6 inhibitors may be continued following COVID-19 exposure, the decision being shared with the patient. In patients with documented COVID-19 infection, the panel suggested that non-IL-6 biologics and JAK inhibitors should be stopped or withheld. IL-6 inhibitors may be continued as a part of a shared decision-making process.[40]

The Global Rheumatology Alliance group have suggested the possible role of anti TNF therapy in protection from severe COVID-19 infection.[13] There is currently no evidence indicating that TNF inhibition is harmful to patients in the context of COVID-19. It is not currently known whether there is any association between rituximab and risk of infection with COVID-19. It has not been associated with significantly increased rates of infections for most rheumatologic indications. The NHS recommends decreasing the dose of rituximab to 1 pulse or delaying intervals between infusions if possible in patients on maintenance treatment.[42]

Table 2 Summary of recommendations from various guidelines regarding use of immunomodulatory therapy during COVID-19

Drugs	Recommendation
Steroids	Use lowest possible dose, avoid sudden discontinuation, methylprednisolone only for major organ failures, moderate dose dexamethasone in moderate to severe COVID-19
csDMARDs	Can be continued, consider stopping SSZ, MTX, LEF in documented/presumptive COVID-19
bDMARDs, tsDMARDs	May initiate therapy in moderate-to-severe rheumatic conditions. Withhold all biologics, except IL-6 inhibitors, in documented/presumptive COVID-19 Consider switching from intravenous to subcutaneous form if available Consider increasing dosing interval or reduction of RTX dose
Pneumococcal and influenza vaccine, vitamin D	Recommended
Immunosuppressants: cyclophosphamide, azathioprine, mycophenolate mofetil, calcineurin inhibitors	Currently not enough evidence to assign risk No specific recommendations to individualize for each patient

Abbreviations: bDMARDs, biological disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; LEF, leflunomide; MTX, methotrexate; RTX, rituximab; SSZ, sulfasalazine; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs.

NICE guidelines recommend giving denosumab, extending dosing intervals to no longer than 8 months. Treatment with zoledronic acid can be postponed for up to 6 months.[42]

More data is however required for evidence-based guidelines. Access to healthcare is also a major issue in our setting, and teleconsultations may be extremely beneficial in patients with chronic diseases who are unable to come to the hospital. This may reduce the risk of hospital exposure to COVID-19 in susceptible patients and enable continuity of care.[43]

In conclusion, COVID-19 has resulted in unexpected challenges in patients with chronic diseases. Rheumatologists need to be aware of the various aspects of diagnosis and treatment of COVID-19. It is still not clear if women with RD and/or on immunomodulatory treatment have an increased risk for severe COVID-19. Evidence is rapidly accumulating but often needs careful interpretation. Till the details of RCTs are available, empirical treatments based on expert opinion may be the most rational way forward.

Conflicts of Interest/Funding/Disclosures
None declared.

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