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## REVIEW ARTICLE

## Inflammatory arthritis in patients with COVID-19

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**Patients with inflammatory arthritis represent a possible high-risk group to COVID-19 due to their immunosuppressive regimen designed to maintain low disease activity. Thus, substantial effort has been put forth to understand the impact of COVID-19 on these patients. Patients with rheumatic diseases as a whole do not appear to be more susceptible to acquiring COVID-19. Furthermore, immunosuppression generally did not increase the likelihood of developing severe COVID-19, with the important exception of medium and high-dose glucocorticoid use. In addition, a small number of COVID-19 patients have developed new inflammatory arthritis; whether this represents an unmasking of previous subclinical disease or a bone fide virus-induced arthritis is unclear. Nevertheless, it appears that inflammatory arthritis patients currently on immunosuppression should continue their medication to prevent future flares and limit glucocorticoid usage. While this continues to be a rapidly evolving field, these data are reassuring to both patients with and providers treating inflammatory arthritides. (Translational Research 2021; 000:1–11)**

**Abbreviations:** ACE-2 = Angiotensin converting enzyme-2; ACR = American College of Rheumatology; C1 = Complement component 1; CI = Confidence interval; COVID-19 = Coronavirus disease-2019; DMARD = Disease-modifying antirheumatic drugs; EULAR = European League Against Rheumatism; GRA = Global Rheumatology Alliance; HCQ = Hydroxychloroquine; HIV = Human immunodeficiency virus; HLA = Human leukocyte antigen; HR = Hazard ratio; MIS-C = Multisystem inflammatory syndrome in children; MRI = Magnetic resonance imaging; NHS = National Health Service; OR = Odds ratio; PCR = Polymerase chain reaction; RA = Rheumatoid arthritis; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; SLE = Systemic lupus erythematosus; SLICC = Systemic Lupus Erythematosus International Collaborating Clinics; TNFi = Tumor necrosis factor inhibitor; TRACR = Trinity Rheumatology and COVID-19 Registry; UK = United Kingdom; US = United States;

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## INTRODUCTION

As of the Fall of 2020, the coronavirus disease-2019 (COVID-19) pandemic continues to persist with over 44 million confirmed cases globally.<sup>1</sup> An early recognized vulnerable group were patients with autoimmune diseases such as rheumatoid arthritis and seronegative spondyloarthritis, as they require immunomodulatory therapies to control their disease severity. This introduced the obvious risk of increased susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the causative agent of COVID-19. The response by medical investigators though has been swift, and within several months, an increased understanding of the risk, impact, and sequelae of COVID-19 on these patients has emerged. Here, we discuss how COVID-19 has impacted those with inflammatory arthritis, including the risk of acquiring COVID-19 and the likelihood of progression to severe disease while on immunosuppressive therapy. We then discuss whether a possible connection between COVID-19 and the initiation of *de novo* inflammatory arthritis exists. Finally, we review management strategies of immunosuppressed patients with inflammatory arthritis based on the best current data available.

## IMPACT OF COVID-19 ON PATIENTS WITH INFLAMMATORY ARTHRITIS

Patients with rheumatic disease are at increased risk of infection.<sup>2,3</sup> This is due to a combination of underlying disease and treatment-related factors.<sup>4-7</sup> It was within this context that, at the beginning of the COVID-19 pandemic, concerns arose regarding the potential consequences of SARS-CoV-2 infection in patients with rheumatic disease. Given the potential negative effects of immunosuppressive drugs on viral clearance, there was concern that infection would be associated with increased COVID-19 severity and excess mortality in patients with rheumatic disease.

Early recommendations advised that rheumatic disease patients were to be considered at high risk and should take appropriate measures to minimize risk of exposure.<sup>8</sup> At the same time, however, the use of immunosuppressive therapies to dampen the dysregulated immune response, which was hypothesized to be a feature of severe COVID-19, became a major focus of investigation.<sup>9</sup> As the course of the pandemic progressed, evidence to better inform decisions regarding immunosuppressive use in rheumatic disease patients has begun to emerge.<sup>10-12</sup> However, considerable uncertainty still exists regarding the management of patients with rheumatic disease in the era of COVID-19. There are two key aspects of the ascertainment of

COVID-19 associated risk in rheumatic disease patients: Firstly, are patients with rheumatic disease at increased risk of SARS-CoV-2 infection and secondly, are rheumatic disease patients with COVID-19 at increased risk of severe disease or mortality?

### **Risk of COVID-19 in patients with inflammatory arthritis.**

The first of these questions, the relative risk of COVID-19 in patients with rheumatic disease, is potentially the more difficult to answer, especially in the context of an emerging infectious disease. Accurate ascertainment of the incidence of COVID-19 in rheumatic disease patients requires a clear denominator population. This has proven difficult to determine accurately in many settings. An additional difficulty is comprehensively assessing any identified denominator population to determine if they have had COVID-19, both in terms of reviewing large numbers of individual patients and the limitations of clinical testing. On a larger scale, there have also been significant challenges determining the incidence of COVID-19 in the population at large; asymptomatic infection, overwhelmed health services, limited testing capacity (particularly for nucleic acid-based testing), and the intrinsic limitations of retrospective methodologies such as antibody testing all play a role in this.<sup>13-15</sup>

However, studies have begun to emerge which are shifting the fog of COVID-19 risk in rheumatic disease patients. The TRACR study evaluated 7500 patients with rheumatic disease, 4524 with inflammatory rheumatic diseases and 2976 with non-inflammatory rheumatic disease, from 2 hospitals in Ireland.<sup>16</sup> 78 cases of polymerase chain reaction (PCR)-confirmed or physician-diagnosed COVID-19 were identified. No significant difference was seen in incidence rates between those with inflammatory rheumatic diseases (1083/100000), noninflammatory rheumatic disease (940/100000) and the general population (887/100000). A study from the initial epicenter in Wuhan, China reported 17 patients with systemic autoimmune diseases among 2804 admissions for COVID-19. The authors noted that this rate of 0.68% was far below what would have been expected given the prevalence of autoimmune diseases in their population (3%-10%).<sup>17</sup> In Hong Kong, which implemented some of the most stringent public health measures against COVID-19 early in the pandemic, a national surveillance program identified 5 PCR confirmed cases of COVID-19 in patients with rheumatic disease as of late May 2020 and reported the estimated incidence of COVID-19 as 0.0126% in patients with rheumatologic diseases compared to 0.0142% in the general Hong Kong population.<sup>18,19</sup> A German study looking at anti-SARS-CoV-2 antibody positivity in 352 rheumatic disease patients found a similar seroprevalence rate of 1.4% to the general

populations seroprevalence of 1.42%.<sup>20</sup> Multiple other studies from Italy, Germany, and the Netherlands also reported no increased risk of clinical COVID-19 in rheumatic disease patients compared to the general population.<sup>21-26</sup>

A smaller number of studies have reported findings suggesting an increased risk of either SARS-CoV-2 infection or COVID-19 in rheumatic disease patients. A Spanish multicenter study retrospectively matched PCR-confirmed COVID-19 cases to 26,131 rheumatology patient records finding 0.76% patients were PCR-positive.<sup>27</sup> There was a higher prevalence in rheumatic disease patients than in the reference population, odds ratio (OR) 1.3 (95%CI 1.15–1.52). The risk appeared most marked in spondyloarthritis (OR 1.54 [95%CI 1.11, 2.13]), giant cell arteritis (GCA)/polymyalgia rheumatica (PMR) (OR 2.53 (95%CI 1.62, 3.93)), systemic immune diseases other than SLE (OR 2.69 (95%CI 1.96, 3.69)), and in those on biologic or targeted synthetic disease-modifying antirheumatic drugs (DMARDs) (OR 1.60 [95%CI 1.23, 2.10]). A study from Tuscany reported an OR of 3.01 (95% CI 1.13–8.09) for anti-SARS-CoV-2 antibodies in 295 biologic DMARD-treated rheumatic disease patients compared to the general population.<sup>28</sup>

An important caveat to the interpretation of this data is that it is difficult to account for possible behavioral differences arising from risk perceptions; if rheumatic disease patients are more likely to reduce social contacts and wear face coverings, for example, then this may affect the accurate estimation of baseline risk. Studies to date have not accounted for this potential confounder. The accurate quantification and subsequent adjustment for the influence of risk-mitigating behavior is difficult, but it is an important limitation of the existing data which must be kept in mind. The relative contribution of specific immunosuppressive drugs as they relate to risk of infection with SARS-CoV-2 is harder to define and remains a focus of ongoing epidemiological studies.

**COVID-19-related health care changes for people with rheumatic disease.** In addition to the risks associated with COVID-19 infection, people with rheumatic disease have also been directly impacted by changes in healthcare delivery and resource allocation during the pandemic. In early 2020, sudden international demand for hydroxychloroquine as an experimental therapy for COVID-19 created widespread shortages.<sup>29,30</sup> An electronic survey sent to 42 Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) members in May 2020 revealed current or prior HCQ shortages in 8 of 13 (62%) countries and 65% of responding SLICC members had been contacted by patients and pharmacies regarding difficulties accessing HCQ.<sup>30</sup>

While some countries took measures to protect local drug supplies for patients who were previously taking the drug, others did not and within the US, regulations about hydroxychloroquine supplies varied by state.<sup>31,32</sup>

In subsequent surveys of people with rheumatic disease regarding COVID-19, difficulty filling prescriptions, concerns about drug supplies, and self-directed medication changes were a common theme regardless of location. In a survey of US rheumatology patients in March 2020, 10% (20/197) were unable to obtain their medications and 14% (28/197) had self-directed changes to prescribed medications or doses in the preceding 2 weeks.<sup>33</sup>

A similar survey in Mexico from a single outpatient center showed 15% (52/345) of respondents reported some form of medication nonadherence, of which 48.1% (25/52) was due to lack of drug availability and 25% (13/52) was due to concerns about contracting COVID-19.<sup>34</sup> In a survey from Saudi Arabia with 591 respondents who were actively taking medication prescribed for rheumatic diseases, 47.9% reported difficulty filling their prescription, 29.5% had self-altered (dose escalation, discontinuation, and reduction) their medications, and 31.9% were unable to attend rheumatology follow up visits due to local quarantine restrictions.<sup>35</sup> While these survey data based data has inherent limitations, it is important for rheumatologists to consider how the COVID-19 pandemic has impacted access to vital medications, rheumatology care, and patient health-related behaviors.

**COVID-19 severity in patients with inflammatory arthritis.** The relative severity of COVID-19 in patients with rheumatic disease compared to the general population has been the focus of several studies. A UK study of 10,387 patients with rheumatic disease found an identical mortality rate from PCR-confirmed COVID-19 to the general population of 0.12%.<sup>36</sup> A case control study of 88 Italian patients with COVID-19 (26 with rheumatic disease and 62 controls) found no increased severity of COVID-19 in rheumatic disease patients.<sup>37</sup> The TRACR study reported equivalent rates of hospitalization between those with systemic rheumatic diseases (15%) and the general population (13%). An Iranian study examined patients admitted with COVID-19-associated pneumonia, comparing 30 patients with autoimmune disease to 381 non-autoimmune disease patients finding no difference in any outcome.<sup>38</sup> Further studies from Italy, Germany, and the Netherlands found no increase in COVID-19 severity in rheumatic disease patients compared to the general population.<sup>22,26,39,40</sup> However, a comparative cohort study from Boston identified 52 rheumatic disease patients who developed COVID-19 and compared these to 104 matched nonrheumatic comparators. A

similar proportion of both groups were hospitalized (44% vs 40%) and mortality was similar (6% vs 4%) but the rheumatic disease patients were significantly more likely to require ventilation (OR 3.11 (95%CI 1.07, 9.05)<sup>41</sup> A comparative study from Wuhan including 21 rheumatic disease patients also showed a higher rate of respiratory failure in the rheumatic disease group (38% vs 10%,  $P < 0.001$ ).<sup>42</sup> An interesting case report demonstrated persistent SARS-CoV-2 infection and viral evolution over five months in a patient with severe antiphospholipid syndrome previously treated with intensive immunosuppression.<sup>43</sup> Whether this was an exceptional circumstance or a wider concern is unclear. Regarding mortality, data from the health analytics platform OpenSAFELY using electronic records from primary care practices for over 40% of NHS patients in England found 10,926 COVID-19 related deaths in 17,278,392 adults (0.06%) as of May 6, 2020. Within this dataset, 878,475 (5.1%) carried a diagnosis of rheumatoid arthritis, SLE, or psoriasis and 962 (0.11%) COVID-19 related deaths occurred (adjusted HR 1.19, 95% CI 1.11–1.27).<sup>44</sup> Overall, these studies suggest that the risk of severe outcomes is either similar or only slightly higher among patients with autoimmune diseases as a whole.

Risk factors for worse COVID-19 outcomes in patients with rheumatic diseases have also been identified. The Global Rheumatology Alliance (GRA) reported on risk factors for hospitalization in the first 600 cases in its provider registry.<sup>45</sup> Similar to the general population, increasing age and nonrheumatic comorbidities such as hypertension and cardiovascular disease emerged as the most significant negative prognostic markers with ORs of between 2 and 3. Medium to high doses of glucocorticoids (prednisolone equivalent of  $\geq 10\text{mg/day}$ ) were a risk factor for hospitalization (OR 2.05 (95% CI 1.06, 3.96)) whilst biologic monotherapy (OR 0.46 (95% CI 0.22, 0.93)) and particular tumor necrosis factor- $\alpha$  inhibitor (TNFi) use (OR 0.40 [95% CI 0.19, 0.81]) appeared protective. A case series from New York of a total of 103 patients with inflammatory arthritis from the same center also suggested a lower risk of hospitalization in those taking biologic DMARDs or janus kinase (JAK) inhibitors and higher risk with glucocorticoids.<sup>46,47</sup> The TRACR study also reported that those receiving biologic DMARDs were significantly less likely to be admitted to hospital.<sup>16</sup> A Spanish study compared 456 patients with rheumatic disease and an equal number of controls, finding that connective tissue diseases but not inflammatory arthritis or immunosuppressive treatments were associated with severe COVID-19.<sup>48</sup> A second Spanish study of 123 patients also suggested that having a systemic autoimmune condition compared to inflammatory arthritis was a risk factor for hospital admission.<sup>49</sup> A US study of

rheumatic disease patients with COVID-19 reported high rates of hospitalization and ventilation among patients with SLE.<sup>50</sup>

Interpreting the available data on the relative severity of COVID-19 would suggest that in general rheumatic disease patients do not appear at increased risk of a more severe disease course; the study from Boston, given the strength of its methodology, does sound a note of caution regarding ventilation rates but at the same time was reassuring regarding mortality. Within the rheumatic disease population some clear risk factors are emerging, particularly medium to high dose glucocorticoids for a prolonged period, and perhaps a diagnosis of connective tissue disease or systemic vasculitis. There is intriguing suggestive data that biologic DMARDs, especially TNFi may be protective. As the pandemic continues unabated it is likely that increasing clarity around these issues will emerge in due course.

#### CAN COVID-19 CAUSE INFLAMMATORY ARTHRITIS? LESSONS LEARNED FROM OTHER VIRUSES

While there is an evolving understanding of the impact of COVID-19 on patients with arthritis, it is less clear whether SARS-CoV-2 infection can also induce an inflammatory joint disease. It is well established that several viruses are associated with the development of acute and/or chronic arthritis. Virus-induced arthritis may be related to the acute stage of virus infection, associated with other symptoms including rash, fever, myalgia, and arthralgia (eg, parvovirus, enteroviruses, rubella). Arthritis associated with acute viral infection is most commonly self-limiting but certain virus-induced arthritis may become chronic (eg, as seen in patients infected with Chikungunya virus, hepatitis B virus, HIV, or parvovirus). Alternatively, certain viral infections may primarily induce a chronic, self-sustaining arthritis (eg, chronic arthritis associated with hepatitis C virus). The immunopathogenic mechanisms of virus-induced arthritis are not conclusively established. Three major mechanisms have been hypothesized to contribute to the development of virus-induced arthritis.

1. Direct viral pathology: There may be evidence of viral presence in synovium and synovial fluid with or without evidence of virus-mediated pathology. Viruses that have been detected in the joint include rubella,<sup>51</sup> parvovirus,<sup>52</sup> enteroviruses,<sup>53</sup> HIV,<sup>54,55</sup> Ross River virus,<sup>56</sup> and Chikungunya,<sup>57</sup> although they are not invariably present in arthritides associated with these specific viruses.
2. Immune complex-mediated inflammation: There are older observations suggesting virus infections may



trigger an immune complex-mediated arthritis (eg, chronic hepatitis B<sup>58</sup>).

3. Immune activation: It is possible that ongoing inflammatory disease due to persistent viral infection (eg, hepatitis C, HIV) may predispose towards autoimmune mediated arthritis.

HIV is worth a particular mention. HIV is associated with acute arthritis during seroconversion, a chronic HIV-associated arthritis that responds to antiretroviral therapy and a seronegative arthritis with associated spondylitis (with or without HLA-B27).<sup>59</sup>

**New-onset inflammatory arthritis in patients with COVID-19.** Unlike other viral infections commonly complicated by transient or chronic arthritis (eg, parvovirus, chikungunya virus, Zika virus, hepatitis C virus, human immunodeficiency virus),<sup>60</sup> non-SARS-CoV-2 coronaviridae have not been linked to the occurrence of inflammatory arthritis. One notable exception is a more recent epidemiological observation linking background respiratory viral infections (including metapneumovirus, coronavirus, and parainfluenza virus) with an increase in the incidence rates of rheumatoid arthritis using insurance claims data in Korea.<sup>61</sup> While non-specific musculoskeletal symptoms, including diffuse arthralgias, frequently accompany acute SARS-CoV-2 infection,<sup>62</sup> the development of inflammatory arthritis in patients with COVID-19 is uncommon, with only a few case reports discussing a temporal association. Despite 44 million confirmed cases of SARS-CoV-2 infection worldwide to date, only 9 cases of acute arthritis - not better explained by a pre-existing rheumatic disease - have been reported in the literature (Table 1). While no single clinical phenotype has emerged from these studies, reported cases to date appear to be enriched in seronegative mono- or oligoarticular disease, not infrequently accompanied by enthesitis/tendonitis, reminiscent of reactive arthritis.<sup>63-68</sup> Achilles tendonitis or enthesitis was present in 2 patients.<sup>63,67</sup> With the exception of a case reported by Danssaert et al. associated with a positive antinuclear antibody with speckled pattern of unknown titer and significance, all patients had seronegative disease (Table 1). HLA-B27 genetic testing was performed and negative (or not reported to be positive) in 2 cases.<sup>63,67</sup> Erosive bone changes were not apparent on either X-ray or magnetic resonance imaging (Table 1). The exact time frame in relation to onset and resolution of COVID-19 symptoms in this group is not universally reported.

Different to the phenotype of reactive arthritis-like disease, De Stefano et al. reported a case of transient seronegative monoarthritis of the elbow in a 30-year-old man with no prior history of rheumatic disease which started 10 days after resolution of his COVID-19

symptoms, accompanied by several psoriasis-like skin plaques. Synovitis of the elbow was confirmed by musculoskeletal ultrasound. HLA-B27 and HLA-C06 were negative. Finally, 2 cases of de novo seronegative inflammatory polyarthritis with onset during acute SARS-CoV-2 infection are reported in the literature.<sup>69,70</sup>

Notably, synovial tissue was biopsied in one patient and showed stromal activation and perivascular and diffuse inflammatory infiltrates consisting of CD68+, CD3+ and CD138+ immune cells of monocyte/macrophage, T cell, and B cell lineages. Tissue staining for SARS-CoV-2 antigen was not reported.<sup>69,70</sup> Across all phenotypes, limited data is available to better characterize the inflammatory arthritis. Synovial fluid analyses were performed in 5 of the 9 reported cases and negative for crystals by polarized microscopy (Table 1), but no information about cell counts and differential observed in the fluid is reported. Importantly, alternative causes, especially in patients with a reactive arthritis-like phenotype, were not universally or comprehensively excluded.

Given the sparsity of data discussed above, no causal relationship between SARS-CoV-2 infection and acute arthritis in patients with COVID-19 has been established. To properly address this question a prospective registry study would be required in order to limit bias and appropriately address the timeline of COVID-19 and inflammatory arthritis diagnosis. Given the paucity of cases reported to date, such a study would likely need to be a large multicenter international study in order to recruit sufficient cases. We are not aware of any current study addressing this issue.

While synovial cells, cartilage, and fibroblasts have been shown to express angiotensin converting enzyme-2 (ACE-2) and transmembrane serine protease 2 (TMPRSS2), required for viral entry, at low level<sup>71</sup> and ACE-2 upregulation in inflamed rheumatoid arthritis synovial tissue,<sup>72</sup> neither SARS-CoV-2 nucleic acids nor infectious virus were detected in the synovial fluid of any of the patients who developed arthritis in the setting of COVID-19.<sup>65,66,73,74</sup> While the sample size is too small to reach definitive conclusions, the current data does not suggest a mechanism of direct viral arthritis in COVID-19. Even in the context of active or recent SARS-CoV-2 infection, other etiologies of acute arthritis (especially in hospitalized patients) need to be carefully considered. In a recent study by López-González et al., crystalline arthritis was confirmed by arthrocentesis in 4 patients hospitalized with COVID-19. All four patients had negative synovial fluid nucleic acid testing for SARS-CoV-2 in this acute setting.<sup>74</sup> The exclusion of gout seems particularly important given its high prevalence in the patient

**Table 1.** Reported cases of inflammatory arthritis in patients with confirmed SARS-CoV-2 infection

	Sex, Age	Onset	Articular involvement	Enthesitis/tenosynovitis/other	Serological status	HLA	Synovial fluid	SARS-CoV-2 nucleic acid testing in SF or synovium	Imaging/ Pathology
<b>Ono et al. 2020</b>	M, 50+	Sub-acute ("ReA")	Oligoarthritis (bilateral ankle arthritis)	right Achilles tendon enthesitis	ANA neg., RF neg., anti-CCP neg.	HLA-B27 neg.	"mild inflammatory", MSU neg., CPPD neg., culture neg.	unknown	X-ray: no erosion
<b>De Stefano et al. 2020</b>	M, 30+	Sub-acute ("PsA"), 10 days post resolution of COVID-19 symptoms	Monoarthritis (right elbow)	Psoriasis-like plaques	ANA neg., ENA ab neg., RF neg., anti-CCP neg.	HLA-B27 neg. HLA-C06-neg.	MSU neg., CPPD neg.	negative for SARS-CoV-2 RNA by RT-PCR	US: synovitis with effusion and positive power Doppler signal
<b>Saricaoglu et al. 2020</b>	M, 73	Sub-acute ("ReA")	"Left 1 <sup>st</sup> MTP, PIP; right 2 <sup>nd</sup> PIP, DIP joints	images with possible dactylitis	RF neg., anti-CCP neg.	unknown	Not tested	unknown	X-ray: no erosion
<b>Liew et al. 2020</b>	M, 47	Acute, ("ReA")	Monoarthritis (right knee)	Penile erythema and pain	unknown	unknown	MSU neg., CPPD neg.	negative for SARS-CoV-2 by PCR and culture	X-ray: OA, effusion, no erosion
<b>Yokogawa et al. 2020</b>	M, 57	Acute	Monoarthritis (right knee), arthralgias (left wrist, right Shoulder, bilateral knees)	none	ANA neg., RF neg., anti-CCP neg.	unknown	MSU neg., CPPD neg.	negative for SARS-CoV-2 by RT-PCR	none
<b>Alivernini et al. 2020</b>	M, 61	Acute	Polyarticular (not specified)	none	RF neg., anti-CCP neg.	unknown	MSU neg., CPPD neg.	unknown	US: effusion, thickened synovium, increased vascularity  Synovial biopsy: stromal activation, oedema, inflammatory perivascular and diffuse infiltrates composed of CD68pos, CD3pos and CD138pos cells

*(continued on next page)*



**Table 1. (Continued)**

	Sex, Age	Onset	Articular involvement	Enthesitis/tenosynovitis/other	Serological status	HLA	Synovial fluid	SARS-CoV-2 nucleic acid testing in SF or synovium	Imaging/ Pathology
<b>Parisi et al. 2020</b>	F, 58	Sub-acute, 25 days after her prodrome of infection	Monoarthritis (ankle)	tendonitis of the Achilles tendon	ANA neg., ENA ab neg., RF neg., anti-CCP neg.	HLA-B27 testing performed, presumably neg.	Not tested	unknown	US: synovial hypertrophy in the tibiotarsal anterior and lateral recess, positive power Doppler signal
<b>Danssaert et al. 2020</b>	F, 37	Acute-sub-acute ("ReA")	Presumably Monoarthritis	Right upper extremity extensor tendonitis	ANA pos. (speckled, unknown titer), RF neg., Lyme antibodies neg.	unknown	Not tested	unknown	MRI: inflammation around the extensor tendons of the second, third, and fourth compartments with mild synovial enhancement of the tendon sheaths
<b>Talarico et al. 2020</b>	M, 45	Acute	Polyarthritis (symmetrical, MCP and PIP joints; right wrist)		RF neg., anti-CCP neg.	unknown	Not tested	unknown	US: slight effusion of the right wrist, bilateral effusion of the fifth proximal interphalangeal joint, no synovial hyperplasia or power Doppler signal
<b>Acute arthritis with known prior history:</b>									
<b>López-González et al. 2020</b>	Case series (n=4)	Acute gout/ acute CPPD					MSU+ (n=3) or CPPD+ (n=1)	Negative in 3, not tested in 1 patient	

*Abbreviations:* ANA, antinuclear antibody; CCP, cyclic citrullinated peptide; CD, cluster of differentiation; CPPD, calcium pyrophosphate dihydrate; DIP, distal interphalangeal; ENA, extractable nuclear antigens; F, Female; HLA, human leukocyte antigen; M, Male; MRI, magnetic resonance imaging; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PsA, Psoriatic arthritis; PsO, Psoriasis; OA, osteoarthritis; PIP, proximal interphalangeal; ReA, Reactive arthritis; RF, Rheumatoid factor; MSU, monosodium urate; PCR, polymerase chain reaction; RT, real-time; US, ultrasonography.

population at increased risk of severe COVID-19 (eg, older men with hypertension, obesity, and other cardiovascular risk factors) and since some SARS-CoV-2 directed antiviral therapies (eg, favipiravir) can increase uric acid levels.<sup>75</sup>

The paucity of cases of new-onset arthritis linked to SARS-CoV-2 is different for children. While children are relatively spared from severe acute COVID-19 compared to adults, they are infrequently affected by the multi-system inflammatory syndrome in children (MIS-C), which is thought to be a post-viral immune-mediated inflammatory syndrome following infection with SARS-CoV-2.<sup>76</sup> Meta-analysis reports that 21% of MIS-C cases have associated musculoskeletal involvement,<sup>77</sup> whereas subsequent case series report up to 35% (8/23) of cases presenting with clinical arthritis.<sup>78</sup> It is important to note that confirmation of a true inflammatory (ie, by synovial fluid analysis, MRI, or ultrasound) was not performed.

Finally, it is notable that complement activation appears to be an important physiologic process in both RA<sup>79</sup> severe COVID-19.<sup>80,81</sup> C1 deposition in cartilage biopsies in RA subjects suggested the activation of the classical pathway,<sup>82</sup> and numerous complement activation products are elevated in the synovial fluid.<sup>83,84</sup> Similarly, complement deposition has been observed in the skin and lungs of deceased COVID-19 patients<sup>85</sup> along with increases in complement activation products in sera.<sup>86</sup> But whereas in RA synovial inflammation ensues, in COVID-19, complement activation along with neutrophil extracellular traps appear to contribute to endothelial activation and microthrombi formation.<sup>80,81</sup> Thus, instead of inflammatory arthritis, a phenotype highly similar to what is observed in antiphospholipid syndrome<sup>87</sup> and thrombotic thrombocytopenic purpura<sup>88</sup> occurs.

## MANAGEMENT OF INFLAMMATORY ARTHRITIS IN PATIENTS WITH COVID-19

Any concern regarding the immunosuppressive effects of medications used to treat rheumatic diseases must be balanced against the known morbidity and mortality associated with inadequate treatment of such conditions. The substantial initial concern around a possible increased risk of severe complications from COVID-19 in patients treated with immunosuppressive drugs has thankfully not transpired. With emerging data, a number of organisations including the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) have published recommendations regarding the management of patients with rheumatic disease during the COVID-19 pandemic.<sup>89,90</sup> As

shown by the evidence described previously, most medications used in rheumatology do not appear to be associated with increased risk of COVID-19. There is no indication at present to change a currently effective long-term medication for rheumatic disease due to concern regarding COVID-19. In fact, such action is potentially deleterious due to the risk of disease flare and the possible subsequent use of glucocorticoids.

Prolonged courses of glucocorticoids at doses of prednisone equivalent 10 mg a day or more have consistently been associated with increased risk of more severe COVID-19 disease.<sup>45</sup> While short term use of such glucocorticoid doses is common in rheumatology, the use of prolonged courses likely to be associated with risk is restricted to severe organ and life-threatening diseases and due to clinical necessity and the lack of alternatives should continue to be employed where appropriate. Importantly, glucocorticoids should not be stopped abruptly and may even require an increase in dose in individuals who develop COVID-19.<sup>89,90</sup> Concern has been expressed regarding the powerful immunosuppressive agents cyclophosphamide and rituximab, both regarding the risk of developing severe COVID-19 and the potential inability to develop a long-term immune response due to B-cell depletion.<sup>91-93</sup> Rituximab, and particularly cyclophosphamide, are less frequently used medications in rheumatic disease, and we therefore have less available data to guide us in the setting of COVID-19. However these treatments are generally restricted to severe disease with limited other options and when necessary, should still be utilized. In conclusion, the data regarding the use of rheumatic disease medications in the setting of the COVID-19 pandemic is largely reassuring. To a large extent the ongoing management of the majority of rheumatic disease patients should not differ substantially from that prior to the COVID-19 pandemic.

## CONCLUSION

In just several months, enough data has been generated to provide a preliminary understanding of the impact of COVID-19 on patients with inflammatory arthritis. In summary, the risk of initial infection with SARS-CoV-2 appears to be similar among patients with rheumatic disease compared to the general population. Disease severity in COVID-19 is either similar or only slightly higher among those with rheumatic disease, and risk appears to be driven largely by risk factors similar to the general population such as older age and comorbidities rather than having the rheumatic disease itself. However, evidence to date suggests that patients using moderate-dose glucocorticoids at baseline may be at risk for more severe

outcomes. Much less information is available though about the possible contribution of COVID-19 to new-onset inflammatory arthritis. There have been only a handful of reported cases of frank synovitis, typically a mono/oligoarticular, seronegative phenotype, reminiscent of ReA. Some other reports have described an acute polyarthritis. It remains largely unclear whether this represents a true virus-induced arthritis, an exposure of pre-existing but subclinical disease, or other etiologies, but notably there has been no evidence of virus in synovial fluid nor any link to HLA-B27 to date.

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