Novel coronavirus disease-2019 (COVID-19) in people with rheumatic disease: Epidemiology and outcomes

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A B S T R A C T

There is concern that people with rheumatic disease, often treated with immunosuppressive or immunomodulatory medication, may be at an increased risk of poor outcomes of novel coronavirus disease-2019 (COVID-19). However, hyperinflammation is a major cause of morbidity and mortality in COVID-19 and treatment with glucocorticoids has been shown to improve outcomes in patients with severe COVID-19. Therefore, uncertainty exists about continuing or withholding immune therapies with the risk of infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This review covers the current knowledge with respect to the risk of infection and outcomes and risk factors for poor outcomes in patients with rheumatic disease. We also discuss data from other immune-mediated diseases and its relevance to patients with rheumatic disease. In addition, we cover the limitations of the research efforts to date and how the current

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knowledge translates into practice guidance. Finally, we discuss our vision of the future research agenda.

Introduction

Coronaviruses are a large family of ribonucleic acid viruses with crown-like spikes on their surface that cause diseases in animals and humans. Most of the hundreds of coronaviruses circulate among animals (e.g., cats, pigs, camels, and bats) but "spillover events" (cross-species virus transmission) can occur when the exposure to other species increases and the natural barriers to infection of new hosts are overcome [1].

Seven coronaviruses are known to infect humans. Four of them — human coronavirus (HCoV)-229E, HCoV-HKU1, HCoV-NL63, and HCoV-OC43 — usually cause mild to moderate upper-respiratory tract illnesses, like the common cold, and they are the most common causes of respiratory tract infection throughout the world [1].

However, over the last two decades, three new highly pathogenic and deadly HCoV have emerged from animal reservoirs, namely the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV-1), the Middle East Respiratory Syndrome coronavirus (MERS-CoV) and the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-1 first emerged in November 2002, in Foshan, China, and no human cases have been reported since May 2004; MERS-CoV first emerged in April 2012, in Zarqa, Jordan, and has been causing periodical endemics mainly in the Middle East regions; and SARS-CoV-2 first emerged in December 2019, in Wuhan, China, and is an ongoing pandemic [1].

Coronavirus disease-2019 (COVID-19), the disease caused by SARS-CoV-2, has caused unprecedented pressure on healthcare systems worldwide. Organ dysfunction can be a consequence of cytotoxic damage (direct injury) and immunological insult (indirect damage) to host cells, with severe disease being characterized by severe and rapidly progressive pneumonia, acute lung injury/acute respiratory distress syndrome, acute kidney injury, thromboembolic events, multisystem inflammatory syndrome, multi-organ failure, and septic shock [1]. Many of the drugs being studied as potential treatments or preventive medications for COVID-19, such as interleukin (IL)-6 inhibitors, IL-1 inhibitors, anti-tumor necrosis factor inhibitors (anti-TNF), Janus Kinase (JAK) inhibitors, hydroxychloroquine, and glucocorticoids [2], are commonly used to treat rheumatic disease.

SARS-CoV-2 has precipitated extensive efforts to clarify the risk of poor outcomes in those with immune system disease, including people with rheumatic disease. Hypothetically, people with (inflammatory) rheumatic disease might have a different COVID-19 phenotype and may be at an increased risk of infection and/or severe COVID-19 for a number of reasons. These include; underlying immune system dysfunction, treatment with immunomodulatory or immunosuppressive drugs, higher levels of comorbidity (e.g., cardiovascular disease and osteoporosis), and extra-articular manifestations of their rheumatic disease with organ vulnerability or dysfunction (e.g., kidney or lung involvement) [1].

In this article, we will review the epidemiology and outcomes of SARS-CoV-2 infection and COVID-19 in patients with rheumatic disease. We also discuss data from other immune-mediated disease and its relevance to patients with rheumatic disease. In addition, we cover the limitations of the research efforts to date and how the current knowledge translates into practice guidance. Finally, we discuss what we believe the future research agenda should include.

Risk of acquiring COVID-19 in patients with rheumatic diseases

The meta-prevalence of COVID-19 in autoimmune disease, including rheumatic disease, was recently estimated in a systematic review and meta-analysis [3]. The meta-analysis included 319,025 patients with autoimmune disease (originating from 62 observational studies from 15 countries), of which 17% (N = 53,038; originating from 26 studies) had rheumatic disease, including rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), other spondyloarthritis, systemic

lupus erythematosus (SLE), Sjögren's syndrome, systemic sclerosis, vasculitis, polymyalgia rheumatica, and other autoimmune-mediated diseases (including Behcet's syndrome, sarcoidosis, and inflammatory myopathies). Seven studies focused exclusively on patients with SLE, Sjögren's syndrome, or systemic sclerosis, and were therefore analyzed separately (N = 1641). The meta-prevalence of COVID-19 in patients with rheumatic disease was 0.9% (95% Confidence interval (CI) 0.5%–1.4%), but higher in studies restricted to patients with SLE/Sjögren's syndrome/systemic sclerosis (3.4%, 95% CI from 1.4% to 8.0%). A comparison with other autoimmune diseases is shown in Table 1.

To determine if the prevalence of COVID-19 in patients with rheumatic disease differed from other subjects, six case-controlled studies [4–9] in rheumatic disease were identified. The meta-analysis of these studies suggested that the odds of COVID-19 in patients with rheumatic disease was significantly higher than in control patients, with an odds ratio (OR) of 1.60 (95% CI 1.13 to 2.25 and p = 0.008). The odds were lower than in patients with psoriasis (OR: 3.43, 95% CI: from 1.68 to 7.01, and p = 0.001), for which only one study was available [10]. The combined rheumatic disease/psoriasis OR was 2.19 (95% CI from 1.05 to 4.58 and p = 0.038). No case-controlled studies in other auto-immune diseases were identified.

Using meta-regression analysis, the same authors also investigated the contributions of clinical and demographic variables (age, sex, obesity, hypertension, diabetes mellitus, presence of one or more comorbidities, and medication class) to the prevalence of COVID-19 [3] These analyses showed that studies with a higher proportion of glucocorticoid use in patients with autoimmune diseases had a higher prevalence of COVID-19 (regression coefficient: 0.020, 95% CI from 0.001 to 0.040, and p = 0.042). The proportion of glucocorticoid intake was particularly high in the patients with SLE/Sjögren's syndrome/systemic sclerosis (60.3%). None of the other variables contributed to the risk of COVID-19, including treatment with conventional synthetic disease-modifying drugs (csDMARDs) like methotrexate, biological (b)DMARDs like anti-TNF and targeted synthetic (ts)DMARDs like Janus kinase inhibitors.

While these prevalence data are important and informative, it should be taken into account that the overall quality of evidence was only moderate because of significant study heterogeneity, namely sample size, diseases included, method of collection, diagnostic ascertainment, geographic location, and the date of collection. Therefore, these data should be interpreted with caution.

General outcomes in rheumatic disease patients

To date, most available data on outcomes for people with rheumatic disease infected with SARS-CoV-2 comes from single center or single country case series or from one large international registry; the COVID-19 Global Rheumatology Alliance (GRA) physician registry [11,12]. Case series have considerable limitations, discussed in detail below, however, the data warrants consideration in terms of reassurance if outcomes do not appear substantially worse, and in terms of hypothesis generation and to direct the focus of ongoing and future research [12]. The data from the GRA registry, given size, and multiple sites with global data collection, will be discussed first.

The COVID-19 GRA physician registry

The COVID-19 GRA physician registry resulted from a rapid collaborative effort of international rheumatologists with data collection launched on 24th March for the Global registry and on 27th

Table 1
Meta-prevalence of COVID-19 in autoimmune disease [3].

Disease group	Meta-prevalence	95% CI	Number of studies	Number of patients
Rheumatic disease	0.9%	0.5%–1.4%	26	53,038
SLE, SS, or SSc	3.4%	1.4%–8.0%	7	1641
Autoimmune hepatic disease	3.6%	0.4%–25.8%	1	138
Psoriasis/autoimmune skin disease	1.1%	0.6%–2.1%	14	12,640
Inflammatory bowel disease	0.3%	0.1%–0.6%	14	251,568
Total: Autoimmune disease in general	**1.1%**	**0.5% – 2.5%**	**62**	**319,025**

SS, Sjögren's syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; and CI, confidence interval.

March for the European registry [12]. Preliminary data, on the first 110 patients, were published only three weeks later [13] with the analysis of the first 600 patients published two months after launch [14]. The registry allows rheumatology physicians to enter de-identified data about people with rheumatic disease and confirmed or highly probable COVID-19 infection in the global or European registries (to comply with data management regulations). Data include patient and disease characteristics, comorbidities, rheumatic medications (cs/b/tsDMARDs), diagnosis, treatment and, when possible, outcomes of COVID-19 infection.

The case series reported by the GRA included 600 cases from 40 countries, although most were from the USA or European countries, entered between 24th March and 20th April 2020 [14]. This series represented people with more severe COVID-19 as nearly half (46%) were hospitalized and 9% (55) died. The cases were mostly female (71%) with median age of 56 years (interquartile range 45−67 years). The commonest rheumatic diseases included RA (38%), SLE (14%), and PsA (12%), with 80% of cases deemed to have low disease activity or remission. Almost three-quarters of cases (73%) had polymerase chain reaction (PCR) confirmed COVID-19 with the diagnosis substantiated in cases hospitalized were older and sicker: significantly more hospitalized patients were >65 years of age (43%) as compared to only 16% of non-hospitalized cases being >65 years. All comorbidities were present more frequently in cases that were hospitalized, including hypertension (45% vs 23%), lung disease (30% vs 14%), diabetes (17% vs 7%), cardiovascular disease (14% vs 7%), and chronic renal insufficiency/end-stage renal disease (12% vs 2%) (all p < 0.01). A higher proportion of patients were on moderate dose glucocorticoids (Prednisone equivalent >10 mg/day) among cases that were hospitalized than those not hospitalized (16% vs 7%). In multivariate regression models with hospitalization as the outcome (Y/N) age, comorbidities and glucocorticoid use prior to COVID-19 all remained associated with hospitalization (Table 2). These findings parallel a larger case series in a single health system in the USA with data collection in a similar period, which also found age and comorbidities that were associated with hospitalization in people with COVID-19 [15]. Further interesting observations about rheumatic disease medications were also made in this case series: people with rheumatic disease treated with b/tsDMARDS *only* had lower odds of hospitalization than that of people on no DMARDs (OR in fully adjusted model 0.46 (95% confidence interval 0.22−0.93 and p < 0.03). This observation was largely

Table 2

Adjusted logistic regression models examining the association between demographic and clinical characteristics and COVID-19 hospitalization status (from [14]).

Characteristic	Adjusted OR (95% CI)	*P*-value
Female	0.83 (0.54,1.28)	0.40
Age >65 years	2.55 (1.62, 4.04)	<0.01
Common rheumatic diagnoses:	*Ref*	−
RA	1.74 (0.95, 3.19)	0.08
SLE	0.93 (0.49, 1.79)	0.82
PsA	1.06 (0.49, 2.31)	0.88
Spondyloarthritis	1.55 (0.66, 3.62)	0.31
Vasculitis	0.94 (0.55, 1.59)	0.81
Other		
Common comorbidities	1.83 (1.21, 2.76))	<0.01
HTN or CVD	2.49 (1.56, 3.98)	<0.01
Lung Disease	2.60 (1.39, 4.88)	<0.01
Diabetes	3.07 (1.24, 7.62)	<0.01
CKD/ESRD		
Medications	*Ref*	−
csDMARD only	1.23 (0.70, 2.16)	0.47
b/tsDMARD only	0.46 (0.23, 0.92)	0.03
csDMARD + b/tsDMARD	0.74 (0.38, 1.46)	0.38
Prednisone-Equivalent	*Ref*	−
None	1.04 (0.65, 1.68)	0.86
1−9 mg/day	2.12 (1.10, 4.08)	0.03
≥10 mg/day		
NSAIDs	0.83 (0.69, 1.00)	0.05

influenced by the inverse association between the use of any anti-TNF therapy and hospitalization (OR 0.40, 95% CI 0.19–0.81, and p = 0.01), a finding also observed in the IBD-SECURE registry [16]. These drug associations will no doubt be a focus of future analysis of the GRA Registry data, which now includes over 5000 cases, providing more ability to explore these associations, and with other outcomes such as ventilation support status and death.

Other cohort studies in rheumatic disease

The following cohort studies include those with over 50 patients with rheumatic disease and a laboratory confirmed or highly suspected COVID-19 diagnosis.

A notable single-center study conducted in Spain at the height of the first wave of COVID-19 infections in March/April 2020 also provides useful information about risks of hospitalization for COVID-19 in people with rheumatic disease [17]. The findings largely parallel those of the GRA registry cohort. People previously attending the rheumatology clinic who had symptomatic COVID-19 were identified through hospital admissions data, laboratory COVID-19 PCR testing data, or routine clinical communications and prospectively recruited with 123 people included in this observational cohort. Electronic health records of participants were reviewed, and data extracted on sociodemographic characteristics, types of autoimmune inflammatory rheumatic disease (AIRD), comorbidities, AIRD treatment, and COVID-19 disease course. Most of the patients were women, with a mean age of 60 years and mean duration of AIRD diagnosis of 10 years. Just under half (44%) of patients were admitted to hospital, with patients admitted having higher mean age (68 years versus 52 years in non-admitted). In a univariable analysis, older age, systemic autoimmune conditions (as compared to chronic inflammatory arthritis, (OR 2.65, 95% CI 1.22–5.7, and p = 0.014)), certain comorbidities (hypertension, diabetes mellitus, lung disease, and heart disease) and higher glucocorticoid doses were all associated with increased odds of admission to hospital. Being female or using non-steroidal anti-inflammatory drugs or anti-TNF drugs were associated with lower odds of hospital admission. In multivariable analysis adjusting for age, gender, and comorbidities, age (OR 1.08, 95% CI 1.04–1.13, and p = 0.00) and systemic autoimmune conditions (as compared to chronic inflammatory arthritis) (OR 3.55, 95% CI 1.30–9.67, and p = 0.01) remained statistically significantly associated with hospital admission while the associations for medications did not. Although 50% of patients were on regular glucocorticoids for at least a month before COVID-19 diagnosis, doses were not recorded so these data may still be congruent with the GRA data, which analyzed the association of hospitalization by glucocorticoid dose [14]. Of note, TNF-inhibitors were used by 14% of this cohort and this study may be underpowered to identify an association with the outcome of hospitalization if one exists.

An early report (July 2020) from a health service spanning the five boroughs of New York, reported outcomes for 86 people diagnosed with COVID-19 during March 2020 who had immune-mediated inflammatory disease, which included 50 people with rheumatic disease [18]. In this study, the incidence of hospitalization was 16% (14 patients) with one patient ventilated and one death. While the use of biological DMARDs for underlying rheumatic disease was not associated with worse outcomes, the use of glucocorticoids was higher among patients hospitalized (4 of 14, 29%) than those that were not (4 of 72 not hospitalized, 6%). Subsequently, the same healthcare network reported a cohort of 103 adults with inflammatory arthritis (RA n = 47 and SpA n = 56) also diagnosed with COVID-19, followed up for a median of 42 days after COVID-19 diagnosis [19]. Data on rheumatic disease and COVID-19 disease were collected by web-based questionnaire, telephone, and hospital chart review of hospitalized patients, as appropriate, to describe the COVID-19 course and examine disease or treatment factors associated with poor outcomes. This cohort had a median age of 53 years (range 28–88 years) and were predominantly female subjects (76%). About a quarter of patients were hospitalized (n = 27 and 26%) and 4 died, with two of these over 70 years, giving an incidence of death in the over 65 years of 12% (2/12) subjects. Chronic oral glucocorticoid use was significantly more common in those requiring hospitalization (37% hospitalized vs. 4% ambulatory and p < 0.001). In the multivariable logistic regression analysis, controlling for age and gender, odds ratios for hospitalization were significant for oral glucocorticoids 21.1 (95% CI from 4.09 to 109.03 and p < 0.001) and JAK inhibitors 6.24

(95% CI from 1.49 to 26.24 and p = 0.01). The relationships that remained for glucocorticoids persisted after adjustment for body mass index and comorbidities but persisted for JAK inhibitors only in people with RA. Reduced, but not statistically significant odds ratios for hospitalization were reported for anti-TNF, IL-17 inhibitors, and methotrexate.

A well-designed comparator cohort study examined outcomes for people with rheumatic disease and PCR-confirmed COVID-19 with matched comparators patient (age, sex, and date of COVID-19 diagnosis) in a single health care service network in Boston, USA [20]. Both groups had a mean age of 63 years and 69% were women. Of the 52 cases with rheumatic disease and COVID-19 identified, 75% were on immunosuppressant medications. Overall, cases with rheumatic disease had similar symptoms of COVID-19 and a similar proportion of patients with and without rheumatic disease were hospitalized (23 [44%] vs 42 [40%] and p = 0.50). While mortality was similar between the two groups (3 [6%] vs 4 [4%], p = 0.69, and OR 1.53 [95% CI 0.33 to 7.11, p = 0.6]), cases with rheumatic disease more often needed intensive care admission and mechanical ventilation (11 [48%] vs 7 [18%] and OR 3.22 [95% CI 1.16 to 8.92, p = 0.023]). Although this is a small study undertaken very early in the COVID-19 first wave in the USA, the likely comprehensive capture of COVID-19 cases in this health system and good quality study design does provide some reassurance that people with rheumatic disease are not at increased risk of death from COVID-19. It does also highlight the need for more information about in-hospital care requirements.

A similar case-control study was reported from a single tertiary referral hospital in the Lombardy region of Italy, again during the peak of the initial wave of infections in late February–May 2020 [21]. The 26 people with rheumatic disease admitted with COVID-19 were matched 1:2 with patients admitted with COVID-19 without rheumatic disease (age, sex, and month of hospital admission). These 26 people with rheumatic disease represent only 1% of the 2292 people with COVID-19 admitted to this hospital in the study period. There were no differences found between cases and controls on the duration of symptoms before admission, duration of admission or severity of chest radiographic changes. There were no statistically significant differences in the incidence of hyperinflammatory syndrome (cases 48% and controls 46%) or death (cases 15% and controls 10%) between cases and controls. This center also reported prospective ascertainment COVID-19 infection by telephone calls to 1525 people with rheumatic disease who would have been scheduled for an in-person rheumatology clinic in the study period. Of these, there were 117 people (8%) with COVID-19; 65 laboratory-confirmed and 57 with symptoms highly consistent with COVID-19. During follow-up, 12 (10%) patients died of COVID-19, with 10 of these confirmed cases. Among confirmed COVID-19 cases, the median age of the 10 deceased patients was higher than those surviving (78·8 years [IQR 75·3–81·3] vs 65·5 years [53·3–74·0] and p = 0·0002) but there was no between group difference in sex, comorbidities, or therapies. This is consistent with age as the major risk factor for death in general populations [22].

The meta-analysis described above reporting meta-prevalence, also reported meta-analysis of outcomes of COVID-19 in patients with rheumatic conditions, including hospitalization and death [3]. In the 62 studies, including 2766 patients with a variety of autoimmune diseases, hospitalization rates for rheumatic disease was 0.54 (95% CI 0.46–0.63), and for the combined diagnoses of SLE, Sjögren's disease, and Systemic sclerosis 0.33 (95% CI 0.20–0.49). Death rate due to COVID-19 was 0.113 (95% CI 0.98–0.13) for rheumatic disease and for SLE, Sjögren's disease, and Systemic sclerosis 0.069 (95% CI 0.032–0.14). Patients with rheumatic disease were older and had more comorbidities than other examined autoimmune diseases, and also had highest hospitalization and mortality rates.

The data to date are generally from small studies, often from a single center. While generally reassuring that outcomes for people with rheumatic disease are not substantially worse than general populations once demographic factors and comorbidities are considered, there are intriguing associations between medication use and outcomes. Examples include the use of moderate dose glucocorticoids associated with higher odds of hospitalization or anti-TNF associated with lower odds of hospitalization [14]. These data warrant further examination in more carefully designed studies. Additionally, data from other disease groups may provide further insights.

Data from other specialties

Studies in gastroenterology

The Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE-IBD) gastroenterology registry was a pioneer in the pandemic response [23]. Initial data on 525 patients with inflammatory bowel disease reported glucocorticoids as a risk for poor outcomes (adjusted OR for death of 11.6, 95% CI 2.09−64.74, and P = 0.005). Other notable findings were increased odds of intensive care ICU (admission), ventilation or death of 3.14 (95% CI 1.28−7.71 and P = 0.01) associated with 5-aminosalicylates/sulfasalazine use [16]. There is biological plausibility for poor outcomes in COVID-19 with sulfasalazine use; in a virtual ligand screening study, sulfasalazine was identified as having high-binding affinity for the SARS-CoV-2 spike protein and papain like protease [24]. Other computational screens have also predicted sulfasalazine as interacting with SARS-CoV-2 [25,26]. Sulfasalazine is used commonly in rheumatoid arthritis and peripheral spondyloarthritis and generally considered a drug with a good infectious side effect profile [27]. Further investigation of these results will be required in other datasets like the C19-GRA registry [28].

Studies in infectious disease

The Emerging Infections Network (EIN) conducted a small observational study (n = 81) in people with a range of immune-mediated diseases from rheumatology, gastroenterology, and multi-system diseases like sarcoidosis [29]. No patients on anti-TNF or Janus kinase inhibitors died (0/19 and 0%) as compared to those on other therapies (9/62 and 15%). Initial positive reports on the efficacy of baricitinib in treating COVID-19, and reports on the potential of anti-TNF therapy are supported by these findings [30,31].

Studies in dermatology

A large French study of 1418 patients on treatments for psoriasis reported no COVID-19 deaths. Patients were using oral agents such as cyclosporine and methotrexate as well as anti-TNF, anti-IL-17, and anti-IL-23 agents. Only 12 patients had PCR-confirmed COVID-19 with an additional 54 having probable disease. Five patients were admitted, three of whom were admitted to the ICU, none died [32].

Studies in neurology

A report of 76 patients with multiple sclerosis from New York with COVID-19 (both PCR confirmed and suspected) had a 24% hospitalization rate and an 11% death rate. This cohort had 34 patients on B cell depleting agents and 5.8% of those patients died [33]. Although a very small report, a series of six patients on teriflunomide, which is the active metabolite of leflunomide, were reported from Lombardy in Italy. Patients all continued therapy throughout, and none of the patients required hospitalization or ICU care [34]. The largest series of multiple sclerosis patients (n = 347) was from France; 12 patients (3.5%) died and 73 patients (21%) were hospitalized. In the multivariate analysis age, comorbidity and disability status predicted poor COVID-19 outcomes, while there was no increased risk of poor outcomes with immunosuppressant use [35].

Data limitations

The immediate impact of the pandemic meant that efforts to collect case data were urgent [36]. Study designs have often been a balance between practicalities for data collection and what could help address pressing questions. As such, data limitations, particularly bias and confounding are important to consider. Bias can be broadly thought of as information bias, selection bias, and confounding. There are also the issues of confounding by indication and channeling bias when examining outcomes associated with drug exposures.

Information bias stems from errors in measurement, which is not likely to be a large issue for registry studies. Selection bias, however, is a major concern when considering voluntary registries. Selection bias arises from the non-random collection of data such as in case reports and registries are particularly prone to selection bias. In this novel coronavirus pandemic, it is particularly relevant because often those who collect and report outcome data are hospital-based and therefore, patient outcomes have the potential to be skewed to the more severe outcomes. This is likely evident in the results from the first report of the C19-GRA where 46% of patients were hospitalized and 9% died [14]. Studies that use random sampling, a case-control design, or comprehensive enrolment (e.g., administrative data) can help provide comparative data [20,21].

Response bias is a type of selection bias. A number of studies have attempted to survey whole populations in an effort to ascertain an incidence rate for COVID-19 infections. The majority of these studies have used telephone-interview surveys or telephone-administered automatic surveys. For example, the study by Zhong and colleagues from Hubei province attempted to contact 10,343 patients with autoimmune disease who were taking immunosuppressant medications [5]. Of the total, 1215 had an invalid phone number or did not answer, and 2900 declined participation or discontinued before survey completion. This gives a participation rate of only 60%. It may be that in the context of the coronavirus pandemic, the ability to participate is correlated to infection rate or severity of infection because people who are unwell, hospitalized, or who have died are less likely to respond. The preliminary data collected with urgency during the first months of the pandemic are invaluable in providing initial knowledge to guide patient care and the advice to patients, however, it seems highly likely that more carefully designed and executed studies over time may provide different insights [37].

The engagement with public health measures and the strictness of physical isolation will impact on the risk of patients with rheumatic disease-acquiring COVID-19. Reports of the behavior of patients with rheumatic disease during the pandemic has suggested that some are adhering to isolation measures more strictly. In both qualitative and quantitative studies, patients with rheumatic disease have reported adherence to public health measures such as isolation and physical distancing [38–40]. This directly impacts on estimates of the absolute risk of patients with rheumatic disease acquiring COVID-19, and should be considered when interpreting these estimates.

Practice implications

Numerous organizations have issued guidance for the pandemic during the pandemic, including the American College of Rheumatology (ACR) and The European League of Associations for Rheumatology (EULAR) [41–43]. Consistent guidance is to follow all local public health advice − physical distancing, hand washing, wearing masks and isolation − to reduce the risk of contracting SARS-CoV-2 [44]. Patients are also advised to continue therapy in the absence of suspected SARS-CoV-2 infection. This is particularly important as moderate dose glucocorticoids are likely to be used for active disease flare and are associated with an increased risk of hospitalization in people with rheumatic disease who develop COVID-19 [14].

Hyperinflammation seems to be a major contributor to the morbidity and mortality of COVID-19, and so there is likely to be an, as yet not clearly defined, role for therapies that suppress the immune system. This has been demonstrated in the outcomes of trial of glucocorticoids [45,46]. Because of the initial interest in anti-interleukin-6 therapies in the treatment of COVID-19, the ACR guidelines state that these therapies may be continued as part of a shared decision-making process. Advice to discontinue oral traditional csDMARDs except hydroxychloroquine or chloroquine seems prudent. The data on the effectiveness of IL-6 inhibitors in randomized trials has been largely disappointing [47]. Further knowledge derived from clinical trials of agents such as JAK inhibitors and anti-TNF may see these agents to also be able to be continued as part of a shared decision-making process, however, this awaits more definitive clinical trial outcome data [2].

Summary and future directions

To date the rheumatology community has shown enormous commitment to collect data to the management of people with rheumatic disease. The range and design of studies examining patients

with rheumatic disease affected reflect the urgency of the pandemic. With time the focus of the next phase of studies will be clearer [37]. There are urgent and rapid efforts to develop a vaccine for SARS-CoV-2, with a strong focus on the safety issues [48,49]. If vaccine development takes an extended period of time or the vaccine is of low efficacy, then the focus will continue to be on the treatment of COVID-19, and how rheumatic diseases and their treatment interact with COVID-19. A new focus could be on the efficacy of vaccines in people with rheumatic disease and modification of vaccine response by rheumatic disease treatments.

There have also been numerous reports of prolonged symptoms after the acute illness of COVID-19 has settled, which is the so called "Long-COVID" [50]. What this entity is and whether it is one or many entities is still to be answered. With potentially in excess of 50 million people infected with COVID-19 in the world, then even a low prevalence of post viral chronic fatigue syndrome or systemic exertion intolerance disease could see millions affected by debilitating symptoms. This would be in addition to the renal, respiratory, and neurological sequelae reported from patients.

Practice points

- The risk factors for poor outcome from general population of age and comorbidity also apply to patients with rheumatic disease
- Some antirheumatic drugs like glucocorticoids may be associated with poorer outcomes but in the absence of known or suspected infection, it is recommended that antirheumatic therapy should be continued unchanged
- Entering patients with rheumatic disease who contract COVID-19 into an appropriate registry will help investigators better determine the drug- and disease-specific issues over time

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Research agenda

- There is a need to study specific classes of medication for their individual risk profiles
- There is a need to study patients with individual rheumatic diseases to clarify whether there is differential risk between rheumatic diseases
- There is a need to study the safety and efficacy of vaccines directed at protecting from SARS-CoV-2 infection and adverse outcomes specifically in patients with rheumatic disease

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