COVID-19: What Do Rheumatologists Need to Know?

Gillian E. Fitzgerald[1] • Sinead Maguire[2] • Nigil Haroon[3,4]

Abstract

Purpose of Review Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) emerged in December 2019, rapidly reaching global pandemic proportions. Coronavirus disease 2019 (COVID-19) has presented unique challenges to the rheumatology community. It is known that many individuals with rheumatic disease are at increased risk of severe disease from other infections, sparking a similar fear for COVID-19. In addition, medications routinely used in rheumatology practice are being trialled as treatments, with the potential for drug shortages for rheumatology patients.
Recent Findings Underlying comorbidities and active disease are associated with worse COVID-19 outcomes in patients with rheumatic disease. Tocilizumab and hydroxychloroquine have not proven to be effective treatments in the management of COVID-19. Telehealth has become an essential tool for the rheumatology community to monitor patients during the pandemic.
Summary In this article, we summarise the available COVID-19 evidence that is of relevance to the rheumatology community. We discuss the risk of contracting COVID-19 in individuals with rheumatic disease, along with presenting features and clinical outcomes. We provide an overview of the treatments for COVID-19 which have significance for rheumatology. We highlight published recommendations which can guide our management of rheumatic disease populations during this pandemic. Finally, we discuss the challenges in delivering effective care virtually and present methods and tools which could be adapted for use.

Keywords COVID-19 · Prevalence · Outcomes · Clinical trials · Tele-medicine

Key Points
• Presence of co-morbidities and high doses of steroids (> 10mg/day) were found to be associated with worse outcomes in COVID-19 in patients with rheumatic diseases
• Previous treatment with DMARDs and JAK inhibitors has not been shown to increase risk of infection or adverse outcomes in COVID-19
• Medications which have proven unsuccessful in treating COVID-19 include hydroxychloroquine, tocilizumab, and remdesivir
• Although prior treatment with high doses of steroids (> 10mg/day) is associated with worse COVID-19 outcomes, steroids have been one of the few efficacious treatments for severe COVID-19 infections
• Current guidelines recommend continuation of treatments for rheumatic diseases in patients who do not have COVID-19
• COVID-19 has led to rapid advances in telehealth with a number of tools developed to assess disease activity during these consultations

This article is part of the Topical Collection on *Spondyloarthritis*

✉ Gillian E. Fitzgerald
  gifitzge@tcd.ie

[1] Department of Rheumatology, Toronto Western Hospital, Toronto, Ontario, Canada

[2] Department of Rheumatology, St James' Hospital, Dublin, Ireland

[3] Medicine and Rheumatology, University of Toronto, Toronto, Ontario, Canada

[4] University Health Network and Mount Sinai Hospital, Scientist, Krembil Research Institute, Toronto, Ontario, Canada

Introduction

The emergence of SARS-CoV-2, and the speed with which it reached pandemic proportions, immediately raised concern amongst the rheumatology community. Many individuals with rheumatic disease are known to be at higher risk of a multitude of infections; would this also prove to be true for COVID-19? How should the rheumatology community respond to this pandemic? How would we keep our patients safe? In addition, it was quickly recognised that the severity of COVID-19 was associated with an overactivation of the immune system, akin to a cytokine storm. Medications that have been part of the arsenal for the management of rheumatic diseases were being touted as 'wonder-drugs' for COVID-19.

In this paper, we aim to review the literature on COVID-19 and rheumatology, beginning with the available evidence regarding the risk of contracting SARS-CoV-2 in individuals with rheumatic disease. We summarise the clinical presentation of COVID-19 in this population, as well as the outcomes of disease. We discuss recommendations that have been published which can guide our management in various scenarios. Moreover, we touch on select medications being used to treat COVID-19, focusing only on those that are of relevance to the rheumatology community. A detailed analysis of the treatment of COVID-19 is outside the scope of this review. Finally, we highlight studies which have reported on virtual delivery of rheumatology care during the pandemic.

Incidence of COVID-19 in Individuals with Rheumatic Disease

Individuals with rheumatic disease, particularly those on immunomodulating treatment, are known to be at higher risk of infection [1–4]. Whether this increased risk translates to COVID-19 is not yet clear, as the bulk of published literature is observational (Table 1). Reassuringly, multiple studies to date describing risk factors for severe COVID-19 in the general population have not included rheumatic disease at baseline as a risk factor [5–9].

Presenting symptoms in individuals with rheumatic disease appear to mirror those in the general population, with fever (65–100%), cough (42–75%) and dyspnoea (25–41%) being most common. Other symptoms which can be present include rhinorrhoea (6–50%), diarrhoea (15–35%), anosmia/ageusia (8–75%), malaise (42–100%) and myalgia (25–50%) [12, 16–20].

Clinical Outcomes with COVID-19 and Rheumatic Disease

Recognising that it was critical to gather as much knowledge as possible in as short a time-frame as possible, the international rheumatology community mobilised at an incredible pace to establish the COVID-19 Global Rheumatology Alliance (C19-GRA), with the aim of collecting, analysing and disseminating information about COVID-19 and rheumatology. Rheumatologists enter data of individuals with rheumatic disease and diagnosed with COVID-19 (either confirmed or presumptive) into C19-GRA. Analysis of the first 600 cases (91% confirmed diagnosis) from 40 countries revealed that 46% of cases were hospitalised and 9% died [21••](Table 2).

Robust data on the risk of contraction of COVID-19 and outcomes in rheumatic disease populations is lacking, with a dominance of observational studies. The available evidence is largely reassuring, although there is a suggestion of an increased risk of respiratory failure, without an increased risk of mortality. Similar to the general population, increasing age and comorbid conditions appear to confer the greatest risk of a poor outcome.

It is reassuring that current research has demonstrated no increased risk of adverse COVID-19 outcomes in patients on DMARDs and biologic therapy [17, 21••, 24]. The C19-GRA reported use of these medications was associated with a lower risk of hospitalisation (Table 2). Use of glucocorticoids, however, is associated with increased risk of hospitalisation [21••, 27].

Recommendations for the Management of Rheumatic Disease in COVID-19

Over the recent months, many rheumatology societies around the globe have published recommendations attempting to address concerns regarding the management of individuals with rheumatic disease in the context of the pandemic [29–33]. These guidelines are all presented as a work in progress, as the available literature is low-quality and not of the typical standard required to draft robust guidelines. Hence it is planned that guidelines should be regularly updated as needed. Guidelines published to date largely agree in the management of individuals with rheumatic disease. Patients are advised to continue their treatment if they do not have suspected or confirmed COVID-19. To reduce patients' risk of contracting COVID-19, attempts should be made to postpone face-to-face consultations with patients with stable rheumatic disease. Intervals between regular blood monitoring could also be increased. If necessary, consultations could take place remotely. EULAR recommend that individuals who have been in contact with a SARS-CoV-2 positive individual should undergo testing [33]. Patients with mild COVID-19 symptoms should have decisions regarding potential changes in DMARD therapy made on a case-by-case basis [33]. In individuals with chronic glucocorticoid treatment, this should be continued. However, in individuals with documented or presumptive COVID-19, ACR recommend stopping immunosuppressants, non-IL-6 inhibitors and JAKi [29]. They

Table 1   COVID-19 prevalence in rheumatic diseases, results from observational studies

Author	Country of origin	Number of participants	Patient population	COVID-19 prevalence
Favalli et al. [10•]	Italy	530	49.6% RA 36.8% SpA 10% JIA	COVID-19 positive: 0.6% ($n = 3$) Mild symptoms: 15.2% ($n = 81$)
Zen et al. [11]	Italy	916	43% SLE 20% ANCA-associated vasculitis 19% systemic sclerosis 12% RA 5% idiopathic Inflammatory myopathy	COVID-19 positive: 0.21% ($n = 2$) 1 suggestive symptom: 16.2% ($n = 148$) 2 suggestive symptoms: 2.5% ($n = 23$)
Michelena et al. [12]	Spain	959	Rheumatic disease on tDMARDs	COVID-19 positive: 1.1% ($n = 11$) Suspected COVID: 9.4% ($n = 90$)
Pablos et al. [13•]	Spain	26,131	41.8% RA 18.3% PsA 16.3% SpA 8.6% SLE 5.3% PMR-GCA IA on csDMARDs 28.9% IA on bDMARDs 22.2%	RA 0.57% PsA 0.57% SpA 0.89% SLE 0.62% PMR-GCA 1.45% IA on csDMARDs 0.53% IA on bDMARDs 0.94% All RMDs 0.76% Reference population 0.58%
Zhong et al. [14••]	China	6228	44.4% RA 31.5% SLE 10.5% Sjogrens 1% IgG4-related disease 3.3% UCTD 9.2% other	COVID-19 positive: 0.43% ($n = 27$) Development of COVID-19 following exposure Underlying RMD (OR 3.32, 95% CI 1.54–7.14) Age (OR 1.03, 95% CI 1.01–1.06)
Ferri et al. [15]	Italy	1641	42% RA 13%PsA 2% AS 27% systemic sclerosis 5% SLE 4% UCTD 1% PM/DM 1% Sjogrens 5% other	COVID-19 positive: 0.7% ($n = 11$) Suspected COVID-19: 0.8% ($n = 14$) COVID-19 positive in reference population 0.3% ($n = 349/100,000$)

ANCA anti-neutrophil cytoplasmic antibody, *AS* ankylosing spondylitis, *bDMARD* biologic DMARD, *CI* confidence interval, *COVID-19* 2019 novel coronavirus, *csDMARD* conventional synthetic disease modifying anti-rheumatic drug, *GCA* giant cell arteritis, *IA* inflammatory arthritis, *IgG4* immunoglobulin G 4, *JIA* juvenile idiopathic arthritis, *OR* odds ratio, *PM/DM* poly/dermatomyositis, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *RMD* rheumatic disease, *SLE* systemic lupus erythematosus, *SpA* spondyloarthritis, *PMR* polymyalgia rheumatica, *UCTD* undifferentiated connective tissue disease

advise that HCQ could be continued in most circumstances. Patients should be encouraged to update their vaccination status, particularly focusing on influenza and pneumococci.

Treatment of COVID-19—The Rise of Rheumatology Drugs

In the early months of COVID-19, evidence supporting treatment options were scant. Safe and effective treatments are urgently needed for the management of COVID-19. Due to the recognition that the severity of COVID-19 is associated with a cytokine storm, many treatments being considered are immunomodulators, who have their origins in the world of rheumatology. Ideally, large multicentre placebo-controlled RCTs are needed to provide clinicians with high-quality data. Currently, a number of treatments are being tested in active trials, such as the UK-based Randomised Evaluation of COVid19 thERapY (RECOVERY) trial [34]; more insights into their use should be forthcoming.

Chloroquine (CQ) and Hydroxychloroquine (HCQ)

Early in the pandemic, there was significant interest in the potential therapeutic benefits of chloroquine (CQ) and

Table 2 Clinical outcomes in patients with RMDs and COVID-19

Author	Patient population	Study design	COVID-19 outcomes
Gianfrancesco et al. [21••]	RA 38% SLE 14% PsA 12% SpA 8% Vasculitis 7% Sjogren's 5% Other IA 4% Inflammatory myopathy 3% Gout 3% Systemic sclerosis 3% PMR 2% Sarcoidosis 2% Other 5%	Global Registry	Hospitalisation rate: 46% ($n = 277$) Mortality: 9% ($n = 55$) Predictors of hospitalisation: Age > 65 (OR 2.56, 95% CI 1.62–4.04) HTN/CVD (OR 1.86, 95% CI 1.23–2.81) Lung disease (OR 2.48, 95% CI 1.55–3.98) Diabetes (OR 2.61, 95% CI 1.39–4.88) CKD (OR 3.02, 95% CI 1.21–7.54) Decreased risk of hospitalisation: Prior tx with DMARDs (OR 0.46, 95% CI 0.22–0.93) Prior tx with anti-TNF (OR 0.40, 95% CI 0.19–0.81) Increased risk of hospitalisation: Tx with prednisolone > 10 mg/day (OR 2.05, 95% CI 1.06–3.96)
D'Silva et al. [20]	RA 37% SLE 19% PMR 13% SpA 13% Myositis 6% Vasculitis 6% Sarcoidosis 2%	Cohort study	63% ($n = 33$) active disease at time of diagnosis 75% ($n = 39$) on immunosuppressive therapy Outcomes in RMD vs controls Hospitalisation rate: 44% vs 40%, $p = 0.50$ ICU Admission & Mechanical ventilation: 48% vs 18%, $p < 0.01$ Mortality: 6% vs 4%, $p = 0.69$
Ye et al. [22]	RA 38% SLE 19% Sjogren's 14.3% UCTD 9.5% PMR 4.8% JIA 4.8% AS 9.5%	Retrospective case series	21 patients with RMDs admitted with COVID-9 Outcomes in RMD vs controls Respiratory failure: 38% vs 10%, $p < 0.001$ Mortality: 57% vs 47%, $p > 0.99$
Zhao et al. [23]	RA 52% SLE 17% Rhupus 3.4% Myasthenia gravis 7% Sjogren's 3% AS 3% Dermatomyositis 3% Autoimmune liver disease 3% UCTD 7%	Retrospective case series	29 patients with RMDs Similar clinical manifestations in RMDs vs those without Patients with RMDs hospitalised 0.95% ($n = 29$) Patients with RMDs requiring ventilation 7% ($n = 2$)
Haberman et al. [17]	Psoriasis 16% PsA 24% RA 23% UC 20% Crohn's 23% AS 10%	Prospective case series	Confirmed COVID-19 69% ($n = 59$) Highly suspected COVID-19 31% ($n = 27$) 72% treated with JAKi or bDMARDs Treatment with bDMARDs or JAKi higher in RMD patients not requiring hospitalisation Most common presenting symptoms: fever and cough Hospitalisation rate: 16% ($n = 14$) Use of glucocorticoids, HCQ & MTX highest in hospitalised patients Admitted patients were older, with comorbidities (HTN, diabetes, COPD) Mortality 7% ($n = 1$)
Santos et al. [24]	RA 39% PMR 21% SLE 14% PsA 11% GCA 7% AS 4% Sjogren's 4% Systemic sclerosis 4%	Prospective observational study	10% of COVID-19 hospitalisations were in patients with underlying RMDs ($n = 38$) Mortality of hospitalised RMD patients: 26% ($n = 10$) Factors associated with increased mortality in RMD: Increased age Arterial HTN (OR 9, 95% CI1–80.8) Dyslipidaemia (OR 12, 95% CI 1.33–108) Diabetes (OR 33, 95% CI 3.46–314) ILD (OR 5.5, OR 1.16–26)

Table 2 (continued)

Author	Patient population	Study design	COVID-19 outcomes
			CVD (6.18 (95% CI 1.1–34.7) Moderate/severe activity of RMD (OR 4.5, 95% CI 0.97–20.7) No significant difference in underlying RMD or previous tx with csDMARDs or bDMARDs and COVID-19 outcomes
Sanchez-Piedra et al. [25]	RMDs treated with bDMARDs or tsDMARDs	Prospective observational registry study	Confirmed COVID-19 75.6% ($n = 31$) Highly suspected COVID-19 24.4% ($n = 10$) Hospitalisation rate: 68.3% ($n = 28$) ICU admission: 14.6% ($n = 6$) Mortality: 7.3% ($n = 3$)
Fredi et al. [26••]	RMDs an MSK disease eligible for telephone survey	Observational case-control study	Confirmed COVID-19 4.3% ($n = 65$) Suspected COVID-19 3.4% ($n = 52$) Hospitalisation rate: 40% (47) Mortality: 10% ($n = 12$) Mortality from COVID-19 in RMD associated with increased age and arterial HTN
Montero et al. [27]	RA 32% SpA 26% Other IA 6% SLE 15% Other CTD 21%	Retrospective observational study	62 patients identified with confirmed COVID-19 Hospitalisation rate: 68% ($n = 42$) Mortality 16% ($n = 10$) Factors associated with hospitalisation: Age > 70 (OR 5.5, 95% CI 1.13–27.1) Male (OR 4.4, 95% CI 1.25–15.39) HTN (OR 5.41, 95% CI 1.53–19.12) CVD (OR 3.89, 95% CI 1.23–12.29) Lung disease (OR 9.14, 95% CI 1.1–75.98) Glucocorticoids dose > 5 mg/day (OR 4.84, 95% CI 1.38–16.95)
Hasseli et al. [28]	RA 45% PsA 18% AS 10% SLE 4% GPA 4% PMR 4% Systemic sclerosis 4% Myositis 3% Sjogren's 1% MCTD 1% GCA 1% Other RMD 7%	National Registry (Germany)	104 RMD patients with COVID-19 At least one co-morbidity: 59% ($n = 61$) Treatment with bDMARDs: 42% ($n = 44$) Hospitalisation rate: 32% ($n = 33$) Mortality: 5.8% ($n = 6$)

AS ankylosing spondylitis, *bDMARD* biologic DMARD, *CI* confidence interval, *CKD* chronic kidney disease, *COVID-19* 2019 novel coronavirus, *COPD* chronic obstructive pulmonary disease, *csDMARD* conventional synthetic DMARD, *CTD* connective tissue disease, *CVD* cardiovascular disease, *DMARD* disease-modifying anti-rheumatic drug, *GCA* giant cell arteritis, *GPA* granulomatous polyangiitis, *HCQ* hydroxychloroquine, *HTN* hypertension, *IA* inflammatory arthritis, *ICU* intensive care unit, *ILD* interstitial lung disease, *JAKi* janus kinase inhibitor, *JIA* juvenile idiopathic arthritis, *MCTD* mixed connective tissue disease, *MSK* musculoskeletal, *MTX* methotrexate, *OR* odds ratio, *PMR* polymyalgia rheumatica, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *RMD* rheumatic disease, *SLE* systemic lupus erythematosus, *SpA* spondyloarthritis, *TNF* tumour necrosis factor, *tsDMARD* targeted synthetic DMARD, *Tx* treatment, *UC* ulcerative colitis, *UCTD* undifferentiated connective tissue disease

hydroxychloroquine (HCQ) in managing COVID-19, which subsequently gained traction in the media. This had unintended consequences, particularly for the rheumatology community, where access to HCQ for those with rheumatic disease that require it for the control of their disease was limited [35]. CQ was reported to have potential therapeutic benefit in SARS-CoV-1 [36], by halting the in vitro replication of SARS-CoV-2 [37] and inhibiting binding of SARS to the cell receptor [38]. The initial hype surrounding HCQ was based on a small open-label non-randomised trial which concluded that HCQ (and azithromycin in a small number of patients) led to quicker viral clearance at day six compared to controls (57% vs 13%), leading the authors to claim a synergistic effect from the combination of HCQ and azithromycin [39]. However, serious concerns regarding the design of this study and analysis of the data collected have been highlighted [40]. More

recently a large observational study of 1446 patients [41] examined the association between HCQ use and intubation or death and found no significant association (HR 1.04, 95% CI 0.82 to 1.32), a finding supported by two further studies [42, 43]. Indeed, there is a concern that HCQ/CQ could in fact be dangerous, and a randomised-controlled trial (RCT) to investigate high- versus low-dosages of CQ was stopped due to higher mortality by day 13 in the high-dose arm, with an increased presence of prolonged QTc interval [44]. An open-label multicentre RCT [45] assigned 665 hospitalised individuals with suspected or confirmed mild-to-moderate COVID-19 of 14 or fewer days of symptoms to standard care, standard care plus HCQ 400 mg twice daily for 7 days, or standard care plus HCQ plus azithromycin 500 mg once daily for 7 days. Primary outcome was clinical status at 15 days. There was no difference in clinical outcomes between the three groups. However, prolonged QT interval was more frequent in those receiving HCQ with azithromycin or HCQ alone. HCQ is used extensively for treating rheumatic diseases with minimal to no significant side effects; however, screening for cardiac adverse events is not routinely done. The reported higher incidence of cardiac events in relation to COVID-19 could be related to the high doses used and the predisposition to arrhythmias especially considering the high IL6 levels that itself can prolong QT interval.

As one of the main mechanisms by which HCQ is proposed to acts is preventing viral entry through ACE2, HCQ may have a role in prophylaxis or early disease; however, recent reports suggest otherwise. A North American study [46] aimed to investigate HCQ in preventing symptomatic infection after exposure to confirmed COVID-19, using a randomised double-blind placebo-controlled trial design. In total 821 participants were recruited and randomised to HCQ or placebo, to begin within 4 days of exposure. Data was self-reported. Primary outcome was symptomatic illness, confirmed by a laboratory test, or COVID-19-related symptoms if testing was unavailable. New COVID-19, developed in 107 (13%) of the participants during the 14-day follow-up. There was no significant difference in the incidence of new COVID-19 illness between the HCQ and placebo group (11.8% vs 14.3%, $p = 0.35$). Adherence was lower in the HCQ group compared to the placebo group (75.4% vs 82.6%, $p = 0.01$). Side effects were higher in the HCQ group (40.1% vs 16.8%, $p < 0.001$) compared to placebo. No cardiac arrhythmias were reported. Notwithstanding the limitations to this study, this study does not provide a case for the use of HCQ as post-exposure prophylaxis for COVID-19. A companion trial [47] aimed to assess whether commencing HCQ in the first few days of symptoms could alter the course of COVID-19 by reducing symptom severity and duration. Investigators enrolled 491 participants with four or fewer days of symptoms plus laboratory-confirmed COVID-19 or COVID-19 symptoms with a confirmed contact. Participants

were randomised to either HCQ (800 mg once, followed by a 600-mg second dose, then 600 mg daily for 4 days) or masked placebo. Initial primary outcome was an ordinal outcome of not hospitalised, hospitalised, intensive care unit stay or death by day 14. Due to low rate of hospitalisation at the first interim analysis, this outcome was modified to change in overall symptom severity over 14 days, measured by a ten-point visual analogue scale (VAS). By day 14, similar rates of symptoms were reported in the HCQ group as placebo (14% vs 56%, $p = 0.21$). There was no significant difference on the VAS scale in the average improvement in symptom severity between the two groups (absolute difference -0.27 points, 95% CI 0.61–0.07 points, $p = 0.117$). Incidence of hospitalisation or death was overall low and did not differ between the two groups ($n = 5$ in HCQ group vs $n = 10$ in the placebo group, $p = 0.29$). Adverse events were again more common in the HCQ group (43% vs 22%, $p < 0.001$), and were predominantly gastrointestinal in origin. A big limitation is the lack of access to laboratory testing to confirm cases of COVID-19. However, this study adds to the body of knowledge disputing the efficacy of HCQ in COVID-19, with no substantial reduction in symptom severity or prevalence over time in non-hospitalised patients with early COVID-19.

With the limitations associated with these trials, the results could perhaps be described as provocative rather than definitive, with the potential prevention benefits yet to be determined. The Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine trial (HERO-HCQ; ClinicalTrials.gov identifier: NCT04334148), a randomised double-blind placebo-controlled trial of approximately 15,000 healthcare workers, is expected to be completed in September and may provide more definitive data on the role of HCQ in the prevention of SARS-CoV-2 infection. Currently, there is insufficient evidence the support the use of CQ/HCQ in either prevention or treatment of COVID-19 and it should not be used outside clinical trials. Stocks of HCQ need to be protected to ensure available supply for those with rheumatic disease [48].

Steroids

The preliminary results of the RECOVERY trial report on the effect of dexamethasone in patients hospitalised with COVID-19 (clinically suspected or laboratory-confirmed) [49]. Participants were randomised 2:1 to receive standard care or standard care plus dexamethasone 6 mg for up to 10 days or hospital discharge. Participants and trial staff were aware of the assigned treatments. Primary outcome was all-cause mortality within 28 days after randomisation. In total, 2104 participants were randomised to dexamethasone and 4321 participants to usual care alone, with a mean age of 66.1 (SD 15.7) years, 36% female and 56% having at least one major co-

existing illness. SARS-CoV-2 infection was laboratory-confirmed in 89%. Mortality at 28 days was significantly lower in the dexamethasone group (rate ratio 0.83, 95% CI 0.75 to 0.93), with the biggest benefit seen in the participants receiving mechanical ventilation (rate ratio 0.64, 95% CI 0.51 to 0.81), followed by those receiving oxygen without invasive mechanical ventilation (rate ratio 0.82, 95% CI 0.72 to 0.94). There was no clear effect amongst patients not receiving any respiratory support (rate ratio 1.19, 95% CI 0.91 to 1.55). Patients with a longer duration of symptoms were more likely to derive a greater mortality benefit with dexamethasone. The authors hypothesise that the benefit seen in participants requiring respiratory support and in those recruited after their first week of illness may suggest that by that stage the disease is dominated by immunopathological elements, with active viral replication playing a lesser role at that stage.

The more recent COVID High-intensity Immunosuppression in Cytokine storm syndrome (CHIC) prospective observational study described 86 patients treated according to a protocol in comparison to 86 matched controls treated with supportive care [50]. Participants had a diagnosis of COVID-19 (clinically suggestive plus positive PCR or chest CT result) and evidence for concomitant cytokine storm syndrome (oxygen saturations ≤ 94% or tachypnoea of > 30/min, plus two out of high CRP, high ferritin or high D-dimer). Treatment protocol consisted of IV methylprednisolone ((MP) 250 mg IV day 1, MP 80 mg IV days 2–5, with an option of a 2-day extension) plus escalation with tocilizumab between days 2 and 5 (single dose of 8 mg/kg to a max of 800 mg) for participants with lack of clinical improvement or worsening in respiratory status, required in 43% of the treatment group. Primary outcome was discharge from hospital or definite clinical improvement. Treatment group had a 79% higher likelihood of achieving definite clinical improvement (HR 1.79, 95% CI 1.20 to 2.67) and on average achieved it 7 days earlier. Hospital mortality was 65% lower in the treatment group (HR 0.35, 95% CI 0.19 to 0.65) and the likelihood to require mechanical ventilation was 71% lower in the treatment group (HR 0.29, 95% CO 0.14 to 0.60). Sensitivity analysis excluding the 43% requiring TCZ revealed that the treatment effects increased, suggesting high-dose steroids can achieve a clinically relevant treatment effect alone.

Both of these studies provide suggestive evidence that glucocorticoids have a role in the treatment of COVID-19, although exactly when they should be started is still not clear.

IL-1 and IL-6 Inhibitors

There is a plausible biological rationale for using IL-6 and IL-1 inhibitors in the treatment of COVID-19. As outlined earlier, severe COVID-19 is associated with a cytokine storm and several studies have demonstrated that IL-1 and IL-6 levels are higher in those with a more severe course of disease [5, 7, 9, 51]. That being said, robust clinical data investigating the use of either IL-1 or IL-6 blockade is limited to date.

Investigators in Milan [52] conducted a retrospective cohort study investigating the benefit of anakinra, an IL-1 inhibitor, in adults with confirmed COVID-19, severe to moderate ARDS and hyperinflammation, managed with non-invasive ventilation. Participants in the anakinra arm received either high-dose ($n = 29$) or low-dose ($n = 7$) subcutaneously. All participants received standard therapy (defined as HCQ and lopinavir/ritonavir), with 16 patients in the control arm. At 7 days, the low-dose arm was stopped due to lack of clinical benefit. Compared with standard treatment, the high-dose anakinra participants had a higher survival rate at 21 days (90% vs 56%, $p = 0.009$). Limitations include lower median age in the anakinra group (62 vs 70 years), the uncontrolled retrospective nature of the study, plus the small numbers. However, the clinical benefit seen with anakinra should prompt further studies to investigate whether it is a true effect.

A retrospective case-control study [53] compared 96 adults with severe to critical COVID-19 disease given a single dose of tocilizumab (TCZ), an IL-6 inhibitor, with a control group of 97 individuals requiring levels of supplemental oxygen that matched the treatment group. Primary endpoint was overall mortality rate. Mortality was reduced in the TCZ group (52% vs 62%), although it did not reach statistical significance ($p = 0.09$). When intubated patients were excluded, mortality was significantly lower in the TCZ group (6% vs 27%, $p = 0.02$), but numbers were small. The retrospective nature of this study comes with several limitations, in particular the lack of matching.

A controlled observational study [54] compared 78 individuals with COVID-19 requiring mechanical ventilation treated with TCZ with 76 individuals who were not. Patients were included if they had severe pneumonia, a laboratory-confirmed COVID-19 diagnosis and required mechanical ventilation. The standard dose of TCZ was a single dose of 8 mg/kg (maximum 80 mg). Primary outcome was survival probability after intubation. Of note, TCZ-treated patients were younger, less likely to have chronic lung or kidney disease and had lower D-dimer levels. Survival was significantly higher amongst TCZ-treated patients ($p = 0.02$) and there was a lower hazard of death, even when controlled for confounders with propensity-score matching (HR 0.54, 95% CI 0.35–0.84). TCZ-treated patients were twice as likely to develop a superinfection (54% vs 26%, $p < 0.001$); however, this did not affect case-fatality ratio (22% vs 15%, $p = 0.42$). Caution is required interpreting these results due to several limitations, including incomplete data, baseline differences between groups and no formalised treatment protocol.

Recently randomised phase 3 trials of IL-6 inhibitors involving TCZ and sarilumab have ended in disappointment [55]. The COVACTA trial for TCZ failed to meet its primary endpoint of improved clinical statues or the secondary

endpoint of decreased mortality, whilst the sarilumab trial was suspended for futility.

Other Immunomodulators

There is a plausible role for the use of TNFα-inhibitors in the treatment of COVID-19 owing to the cytokine storm, but to date, there is a lack of clinical evidence. JAK-inhibitors may also reduce the cytokine drive seen in COVID-19 by targeting those cytokines that are dependent on JAK-signalling [56]. Again, clinical data is lacking. An open-label trial was conducted [57] examining the safety and clinical impact of baricitinib 4 mg/day added to standard of care (lopinavir/ritonavir plus HCQ) in twelve adults with moderate COVID-19 pneumonia. The control group ($n = 12$) received standard of care only. Baseline median CRP was significantly higher in the baricitinib group (8.2 vs 4, $p = 0.002$). Patients in the baricitinib group experienced significantly more clinical improvement by week two than the control group. Discharge occurred in 58% of the baricitinib group vs 8% of the control group at week 2 ($p = 0.027$). No ICU admission was required the baricitinib group, compared to 33% of controls.

Remdesivir

Analysis of the role of anti-viral agents, specifically remdesivir, is outside the scope of this article; however, as one of the few recommended treatments for COVID-19 [58], it would be remiss to not mention it at all. Remdesivir inhibits viral replication through premature termination of RNA transcription. The Adaptive Covid-19 Treatment Trial (ACTT-1) [59] was a phase 3 double-blind RCT comparing remdesivir to placebo in 1062 adults hospitalised with COVID-19 with evidence of lower respiratory tract involvement. Those in the remdesivir arm recovered more quickly than those in the placebo arm, median 10 days (95% CI 9 to 11) vs 15 days (95% CI 13 to 18), with no safety signals identified. A second RCT of 237 patients comparing remdesivir to placebo showed a numerically quicker time to clinical improvement in the remdesivir group in patients with symptoms of less than 10 days, but this did not reach statistical significance [60]. However, the study was terminated prior to attaining the prespecified sample size, as the outbreak was brought under control in the recruiting area; therefore, the final numbers were perhaps underpowered to detect a significant difference. A pharma-sponsored trial investigated the difference between 5 and 10 days of treatment in an RCT of 397 hospitalised patients and found no significant difference in clinical improvement between the two groups [61].

The World Health Organization's (WHO) recently released interim results of the SOLIDARITY trial [62••] which was a large multi-national randomised trial on the effects of remdesivir in addition to three other prominent anti-viral agents. The primary endpoint was in-hospital mortality in moderate to severe COVID-19 infections in hospitalised patients. The analysis showed no significant reduction in hospitalisation, ventilation initiation or duration of hospitalisation in patients treated with remdesivir. The WHO is now considering expanding the SOLIDARITY trial to explore other potential treatment options for COVID-19.

Tele-Medicine in Rheumatology

The rapid lockdown of societies globally forced rheumatologists to quickly devise innovative and effective strategies to allow them to continue providing care to their patients. Physical visits to clinic settings were largely switched to virtual consultations, with the dual aim of reducing the burden on acute healthcare systems and prioritising the safety of patients, staff and society. A survey completed by 221 members of the Indian Rheumatology Association revealed that 51.6% had adopted virtual consultations in March 2020, with only 10% continuing their clinics [63, 64]. Of the rheumatologists who were delivering virtual care, the majority used WhatsApp (51.6%), with the remainder using emails (22.8%) or video consultations (27.1%).

This switch to virtual delivery was borne out of necessity, with little knowledge of their effectiveness. A rheumatology department of an Italian hospital reported their experience of conducting 105 tele-rheumatology visits for individuals with PsA undergoing therapy with biologic ($n = 91$) or targeted synthetic DMARDs ($n = 14$) [65]. The consultations were supported by secure transmission of supplemental information such as laboratory tests. Patients were also invited to upload pictures of suspected active articular or cutaneous manifestations. In 94 patients, therapy was continued, with NSAIDs added in ten cases if clinically indicated. Evidence of active arthritis or enthesitis on review, supported by photos, led to an in-person visit that or the following day, required in only ten patients. This study demonstrates that tele-rheumatology has a role in reducing face-to-face visits during a pandemic.

As this pandemic is unfortunately likely to continue for the foreseeable future, it is important to understand whether virtual delivery of care is acceptable to patients. The rheumatology department of a Spanish hospital surveyed 644 patients to evaluate their satisfaction with phone consultation and the profile of patients who considered phone consultations to be helpful [66]. Of the 37.9% of patients who had received a phone consultation throughout confinement, 52.7% considered that phone consultation could be useful in the monitoring of rheumatic disease. Individuals who considered the phone consultation useful tended towards being younger (44.9 vs 48.4 years, $p = 0.059$) and had significantly ($p < 0.05$) lower levels of axial pain, peripheral stiffness and axial stiffness.

Gender, diagnosis or treatment had no bearing on whether a person found the phone consultation useful.

One difficulty with the virtual care is the inability to undertake a clinical examination, critical for the accurate assessment of joints. In RA, there is an abundance of evidence supporting a treat-to-target approach [67], which utilises a composite measure of disease activity that includes joint counts, such as the disease activity score (DAS28-CRP). The rheumatoid arthritis impact of disease (RAID) score is a patient-derived score with seven items assessing pain, fatigue, functional disability, sleep, coping, physical and emotional well-being, which is validated, reliable and sensitive to change [68, 69]. Patients can complete this score at home, thus making it potentially suitable for use in virtual clinics. A RAID score of < 2 is regarded as a patient acceptable state [70]. A UK-based study explored the association between a RAID score and DAS-28 using mixed-effects regression analysis and found that 97% of patients with a RAID score < 2 had remission as defined by DAS28-CRP < 2.4 [71]. This study provides rheumatologists with reasonable confidence that RAID could be adapted to a virtual clinic, whereby a patient reporting a RAID of < 2 would have achieved a DAS28-CRP of < 2.4.

Another potential useful tool in virtual care is the Flare Assessment in Rheumatoid Arthritis (FLARE) questionnaire, which was developed and validated with the aim of detecting RA flare [72]. This instrument is self-administered by patients and contains 13 statements, with a Likert-scale response. Cut-offs to detect a flare and need for treatment adjustment have been developed, with acceptable discriminative capacity [73]. It has also been compared to the DAS28-CRP and found to be useful in ruling out a flare [74]. An RCT tested the ability of the FLARE-RA in 275 individuals to monitor disease activity compared to outpatient follow-up. Participants were randomised to patient-reported outcome (PRO)-based tele-health follow-up with a rheumatologist, PRO-based tele-health follow-up with a nurse or conventional physician-led follow-up [75]. Tele-health groups were scheduled for a tele-phone consultation every 3–4 months. It was pre-determined that individuals in the tele-health group would require a physical consultation if the FLARE-RA score was ≥ 2.5 or the CRP was ≥ 10 mg/dl. The primary outcome was the DAS28 score. Mean number of visits to the outpatient clinic was 4.15 (SD 1) in the control group, 1.75 (SD 1.03) in the rheumatologist tele-health group and 1.72 (SD 1.03) in the nurse tele-health group. The study discovered that tight control of disease activity in RA obtained by PRO-based tele-health follow-up was not inferior to conventional outpatient follow-up in patients with low disease activity or remission. The tele-health groups had more than a 50% reduction in face-to-face consultations. Both findings are reassuring for rheumatologists attempting to rapidly switch to a virtual-based care setting. Overall, telehealth was received positively by patients [76]. However, concerns existed regarding the absence of face-to-face contact with healthcare professionals. Patients also differed in their acceptance of tele-health, described by Knudsen et al. [76] as the 'keen' and 'reluctant' patient, and more research is needed to assist physicians in how to best accommodate the different values and preferences of patients.

An Italian group [77] conducted a 24-month retrospective observational study examining whether self-reported flares (SRF) by patients with RA could predict radiographic progression. SRF were defined as any worsening of the disease in between visits reported by patients. Short flares (SF) were defined as a DAS28 ≥ 2.6 or an increase of > 0.6 from the previous visit, as assessed by the physician at a visit. SRF were predictors of radiographic progression in a multivariable regression model (OR 3.63, 95% CI 1.16 to 11.36), whereas SF were not (OR 2.78, 95% CI 0.70 to 11.10). This study has several limitations, including its retrospective nature and small number of participants experiencing radiographic progression, but is reassuring that in a world where virtual medicine has become essential, self-report by individuals with RA appears to have clinical utility. Additionally, a systematic review and meta-analysis synthesised the results of 18 articles and found that the correlation between patients with RA and assessors for tender joint counts was 0.61 (95% CI 0.47 to 0.75) and for swollen joints was 0.44 (95% CI 0.15 to 0.73), with the use of a homunculus yielding better results than text format [78].

There is a paucity of data reporting on self-report in other rheumatic diseases. A study of 140 individuals with PsA demonstrated poor correlation between patient and physician scores for tender and swollen joints [79]. Although agreement between physician and patient was better for deformed joints and severity of psoriasis, it still did not reach a clinically useful level of agreement.

In SLE, the Brief Index of Lupus Damage (BILD) is a patient-reported tool, administered by an interviewer via phone or in person and validated against the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) [80]. It has been adapted to a self-administered format (SA-BILD) [81]. The BILD has been shown to be both sensitive to change in disease status and a predictor of mortality [82] and could be a useful tool to assess individuals with SLE through tele-medicine.

PROs such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [83], Bath Ankylosing Spondylitis Functional Index (BASFI) [84], the Ankylosing Spondylitis Quality of Life (ASQoL) measure [85] and the Health Assessment Questionnaire (HAQ) [86] are key in the assessment and management of axial spondyloarthritis (axSpA) and could be adapted to be performed virtually. Assessing spinal mobility represents more of a challenge in virtual models of care, but could potentially be grossly assessed over video; however, to our knowledge, this has not yet been validated against the Bath Ankylosing Spondylitis Metrology Index (BASMI).

Conclusion

The face of medicine has changed beyond recognition over the last few months. The emergence of COVID-19 led to an international mobilisation of the medical and scientific community, with a need to publish and share data, with as much speed as possible. As a result, the rheumatology literature is understandably dominated by observational data to date, with inherent bias. However, the available evidence is largely reassuring. Although there is a suggestion of an increased risk of respiratory failure in individuals with rheumatic disease, this was not accompanied by an increased risk of mortality. Similar to the general population, increasing age and the presence of comorbid conditions appear to confer the greatest risk of a poor outcome in individuals with rheumatic disease. Biologics do not appear to increase the risk of severe disease, although the use of glucocorticoids likely does. However, it cannot be out-ruled that preventative measures taken by individuals with rheumatic disease may have been a significant factor in all these studies.

It is still early days in this pandemic; we cannot afford complacency when it comes to managing the health of individuals with rheumatic disease.

Compliance with Ethical Standards

Conflict of Interest   Nigil Haroon has received honorarium from Abbive, Eli Lilly, Janssen, Novartis and UCB. GF and SM have nothing to disclose.

Human and Animal Rights Statements   This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford). 2011;50(1):124–31.
2. Meroni PL, Zavaglia D, Girmenia C. Vaccinations in adults with rheumatoid arthritis in an era of new disease-modifying anti-rheumatic drugs. Clin Exp Rheumatol. 2018;36(2):317–28.
3. Strand V, Ahadieh S, French J, Geier J, Krishnaswami S, Menon S, et al. Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials. Arthritis Res Ther. 2015;17:362.
4. Petri M. Infection in systemic lupus Erythematosus. Rheum Dis Clin N Am. 1998;24(2):423–56.
5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–62.
6. Sun H, Ning R, Tao Y, Yu C, Deng X, Zhao C, et al. Risk factors for mortality in 244 older adults with COVID-19 in Wuhan, China: a retrospective study. J Am Geriatr Soc. 2020;68(6):E19–e23.
7. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:m1091.
8. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA. 2020;323(16):1574–81.
9. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.
10.• Favalli EG, Ingegnoli F, Cimaz R, Caporali R. What is the true incidence of COVID-19 in patients with rheumatic diseases? Ann Rheum Dis. 2020. https://doi.org/10.1136/annrheumdis-2020-217615. **Favalli et al. published this article as one of the first studies available on COVID-19 in RMDs, in the early stages of the pandemic. This demonstrated a low incidence of the virus in RMD patients**.
11. Zen M, Fuzzi E, Astorri D, et al. SARS-CoV-2 infection in patients with autoimmune rheumatic diseases in northeast Italy: A crosssectional study on 916 patients. J Autoimmun. 2020. https://doi.org/10.1016/j.jaut.2020.102502.
12. Michelena X, Borrell H, López-Corbeto M, López-Lasanta M, Moreno E, Pascual-Pastor M, et al. Incidence of COVID-19 in a cohort of adult and paediatric patients with rheumatic diseases treated with targeted biologic and synthetic disease-modifying anti-rheumatic drugs. Semin Arthritis Rheum. 2020;50(4):564–70.
13.• Pablos JL, et al. Prevalence of hospital PCR-confirmed COVID-19 cases in patients with chronic inflammatory and autoimmune rheumatic diseases. Ann Rheum Dis. 2020;79(9):1170–3. https://doi.org/10.1136/annrheumdis-2020-217763. **Pablos et al. published this large population study on incidence of COVID-19 in hospitalised patients with RMDs which included details on incidence in patients on DMARDs, which was very similar to that of the reference population**.
14.•• Zhong J, Shen G, Yang H, Huang A, Chen X, Dong L, et al. COVID-19 in patients with rheumatic disease in Hubei province, China: a multicentre retrospective observational study. Lancet Rheumatol. 2020;2(9):e557–e64. **Zhong et al. constructed a mutlicenter retrospective review of patients with RMD in China which suggested RMD might increase susceptibility to COVID-19.**
15. Ferri C, Giuggioli D, Raimondo V, L'Andolina M, Tavoni A, Cecchetti R, et al. COVID-19 and rheumatic autoimmune systemic diseases: report of a large Italian patients series. Clin Rheumatol. 2020;39(11):3195–204. https://doi.org/10.1007/s10067-020-05334-7.
16. Gianfrancesco MA, Hyrich KL, Gossec L, Strangfeld A, Carmona L, Mateus EF, et al. Rheumatic disease and COVID-19: initial data from the COVID-19 Global Rheumatology Alliance provider registries. Lancet Rheumatol. 2020a;2(5):e250–3. https://doi.org/10.1016/S2665-9913(20)30095-3.

17. 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;383:85–8.

18. 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):667–8.

19. Cheng C, Li C, Zhao T, Yue J, Yang F, Yan Y, et al. COVID-19 with rheumatic diseases: a report of 5 cases. Clin Rheumatol. 2020;39(7):2025–9. https://doi.org/10.1007/s10067-020-05160-x.

20. D'Silva KM, Serling-Boyd N, Wallwork R, Hsu T, Fu X, Gravallese EM, et al. Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: a comparative cohort study from a US 'hot spot'. Ann Rheum Dis. 2020;79(9):1156–62. https://doi.org/10.1136/annrheumdis-2020-217888.

21.•• Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, et al. 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. 2020b;79(7):859–66. https://doi.org/10.1136/annrheumdis-2020-217871. **Gianfrancesco et al. released these much anticipated results from the Global Rheumatology Alliance demonstrating increased risk of hospitalisation in those with co-morbidities and decreased risk in prior treatment with DMARDs and TNF inhibitors**.

22. Ye C, Cai S, Shen G, Guan H, Zhou L, Hu Y, et al. Clinical features of rheumatic patients infected with COVID-19 in Wuhan, China. Ann Rheum Dis. 2020;79:1007–13.

23. Zhao J, Pang R, Wu J, Guo Y, Yang Y, Zhang L, et al. Clinical characteristics and outcomes of patients with COVID-19 and rheumatic disease in China 'hot spot' versus in US 'hot spot': similarities and differences. Ann Rheum Dis. 2020. https://doi.org/10.1136/annrheumdis-2020-218183.

24. Santos CS, Morales CM, Álvarez ED, Castro C, Robles AL, Sandoval TP. Determinants of COVID-19 disease severity in patients with underlying rheumatic disease. Clin Rheumatol. 2020;39(9):2789–96.

25. Sanchez-Piedra C, Diaz-Torne C, Manero J, Pego-Reigosa JM, Rúa-Figueroa Í, Gonzalez-Gay MA, et al. Clinical features and outcomes of COVID-19 in patients with rheumatic diseases treated with biological and synthetic targeted therapies. Ann Rheum Dis. 2020;79(7):988–90.

26.•• Fredi M, Cavazzana I, Moschetti L, Andreoli L, Franceschini F. COVID-19 in patients with rheumatic diseases in northern Italy: a single-centre observational and case-control study. Lancet Rheumatol. 2020;2(9):e549–e56. **Fredi et al. published the experience of Italy in the height of the pandemic and showed presence of underlying co-morbidity and increased age was more associated with adverse COVID-19 outcomes than rheumatic diseases.**

27. Montero F, Martínez-Barrio J, Serrano-Benavente B, González T, Rivera J, Molina Collada J, et al. Coronavirus disease 2019 (COVID-19) in autoimmune and inflammatory conditions: clinical characteristics of poor outcomes. Rheumatol Int. 2020;40(10):1593–8.

28. Hasseli R, Mueller-Ladner U, Schmeiser T, Hoyer BF, Krause A, Lorenz HM, et al. National registry for patients with inflammatory rheumatic diseases (IRD) infected with SARS-CoV-2 in Germany (ReCoVery): a valuable mean to gain rapid and reliable knowledge of the clinical course of SARS-CoV-2 infections in patients with IRD. RMD Open. 2020;6(2):e001332. https://doi.org/10.1136/rmdopen-2020-001332.

29. Mikuls TR, Johnson SR, Fraenkel L, Arasaratnam RJ, Baden LR, Bermas BL, et al. American College of Rheumatology Guidance for the Management of Rheumatic Disease in Adult Patients During the COVID-19 Pandemic: Version 1. Arthritis Rheum. 2020;72(8):1241–51. https://doi.org/10.1002/art.41301.

30. Richez C, Flipo RM, Berenbaum F, Cantagrel A, Claudepierre P, Debiais F, et al. Managing patients with rheumatic diseases during the COVID-19 pandemic: The French Society of Rheumatology answers to most frequently asked questions up to May 2020. Joint Bone Spine. 2020;87(5):431–7. https://doi.org/10.1016/j.jbspin.2020.05.006.

31. 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):840–2.

32. Tam LS, Tanaka Y, Handa R, Chang CC, Cheng YK, Isalm N, et al. Care for patients with rheumatic diseases during COVID-19 pandemic: a position statement from APLAR. Int J Rheum Dis. 2020;23:717–22.

33. Landewé RB, Machado PM, Kroon F, Bijlsma HW, Burmester GR, Carmona L, et al. EULAR provisional recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2. Ann Rheum Dis. 2020;79(7):851–8.

34. Randomised Evaluation of COVID-19 Therapy. RECOVERY Trial. 2020 [cited 2020 30/06/2020]; Available from: https://www.recoverytrial.net/. Accessed 11 Aug 2020.

35. Mendel A, Bernatsky S, Thorne JC, Lacaille D, Johnson SR, Vinet É. Hydroxychloroquine shortages during the COVID-19 pandemic. Ann Rheum Dis. 2020. https://doi.org/10.1136/annrheumdis-2020-217835.

36. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases. Lancet Infect Dis. 2003;3(11):722–7.

37. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269–71.

38. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2005;2(1):69.

39. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56(1):105949. https://doi.org/10.1016/j.ijantimicag.2020.105949.

40. Kim AHJ, Sparks JA, Liew JW, Putman MS, Berenbaum F, Duarte-García A, et al. A rush to judgment? Rapid reporting and dissemination of results and its consequences regarding the use of hydroxychloroquine for COVID-19. Ann Intern Med. 2020;172:819–21.

41. Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med. 2020;382(25):2411–8.

42. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ. 2020;369:m1849.

43. Mahévas M, Tran VT, Roumier M, Chabrol A, Paule R, Guillaud C, et al. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. BMJ. 2020;369:m1844.

44. Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. JAMA Netw Open. 2020;3(4):e208857.

45. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, et al. Hydroxychloroquine with or without

azithromycin in mild-to-moderate Covid-19. N Engl J Med. 2020;383:2041–52.

46. Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. N Engl J Med. 2020;383: 517–25.

47. Skipper CP, Pastick KA, Engen NW, Bangdiwala AS, Abassi M, Lofgren SM, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial. Ann Intern Med. 2020;0(0):null.

48. McInnes IB. COVID-19 and rheumatology: first steps towards a different future? Ann Rheum Dis. 2020;79(5):551–2.

49. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med. 2020. https://doi.org/10.1056/NEJMoa2021436.

50. Ramiro S, Mostard RLM, Magro-Checa C, van Dongen CMP, Dormans T, Buijs J, et al. Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome: results of the CHIC study. Ann Rheum Dis. 2020;79(9): 1143–51. https://doi.org/10.1136/annrheumdis-2020-218479.

51. Aziz M, Fatima R, Assaly R. Elevated interleukin-6 and severe COVID-19: a meta-analysis. J Med Virol. 2020;92:2283–5.

52. Cavalli G, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. Lancet Rheumatol. 2020;2(6):e325–e31.

53. Rojas-Marte GR, Khalid M, Mukhtar O, Hashmi AT, Waheed MA, Ehrlich S, et al. Outcomes in patients with severe COVID-19 disease treated with tocilizumab - a case- controlled study. QJM. 2020;113:546–50.

54. Somers EC, Eschenauer GA, Troost JP, Golob JL, Gandhi TN, Wang L, et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. Clin Infect Dis. 2020:ciaa954. https://doi.org/10.1093/cid/ciaa954.

55. Furlow B. COVACTA trial raises questions about tocilizumab's benefit in COVID-19. Lancet Rheumatol. 2020;2(10):e592.

56. Spinelli FR, Conti F, Gadina M. HiJAKing SARS-CoV-2? The potential role of JAK inhibitors in the management of COVID-19. Sci Immunol. 2020;5(47):eabc5367. https://doi.org/10.1126/sciimmunol.abc5367.

57. Cantini F, Niccoli L, Matarrese D, Nicastri E, Stobbione P, Goletti D. Baricitinib therapy in COVID-19: A pilot study on safety and clinical impact. J Infect. 2020;81(2):318–56. https://doi.org/10.1016/j.jinf.2020.04.017.

58. National Institutes of Health. COVID-19 Treatment Guidelines. 2020 [cited 2020 29 July]; Available from: https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/remdesivir/. Accessed 4 Aug 2020.

59. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of Covid-19 - final report. N Engl J Med. 2020;383:1813–26.

60. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395(10236):1569–78.

61. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med. 2020;383:1827–37.

62.•• Pan H, Peto R, Abdool Karim Q, Alejandria M, Henao Restrepo AM, Hernandez Garcia C, et al. Repurposed antiviral drugs for COVID-19; interim WHO SOLIDARITY trial results. medRxiv. 2020:2020.10.15.20209817. **Pan et al. report on data from the SOLIDARITY trial which showed no benefit of 4 antiviral agents, including Remdesivir, in treatment of COVID-19.**

63. Gupta L, Misra DP, Agarwal V, Balan S, Agarwal V. Management of rheumatic diseases in the time of covid-19 pandemic: perspectives of rheumatology practitioners from India. Ann Rheum Dis. 2020a:annrheumdis-2020-217509. https://doi.org/10.1136/annrheumdis-2020-217509.

64. Gupta L, Misra DP, Agarwal V, Balan S, Agarwal V. Response to: 'Telerheumatology in COVID-19 era: a study from a psoriatic arthritis cohort' by Costa et al. Ann Rheum Dis. 2020b:annrheumdis-2020-217953. https://doi.org/10.1136/annrheumdis-2020-217953.

65. Costa L, Tasso M, Scotti N, Mostacciuolo E, Girolimetto N, Foglia F, et al. Telerheumatology in COVID-19 era: a study from a psoriatic arthritis cohort. Ann Rheum Dis. 2020:annrheumdis-2020-217806. https://doi.org/10.1136/annrheumdis-2020-217806.

66. López-Medina C, Escudero A, Collantes-Estevez E. COVID-19 pandemic: an opportunity to assess the utility of telemedicine in patients with rheumatic diseases. Ann Rheum Dis. 2020: annrheumdis-2020-218008. https://doi.org/10.1136/annrheumdis-2020-218008.

67. Stoffer MA, Schoels MM, Smolen JS, Aletaha D, Breedveld FC, Burmester G, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update. Ann Rheum Dis. 2016;75(1):16–22.

68. Gossec L, Paternotte S, Aanerud GJ, Balanescu A, Boumpas DT, Carmona L, et al. Finalisation and validation of the rheumatoid arthritis impact of disease score, a patient-derived composite measure of impact of rheumatoid arthritis: a EULAR initiative. Ann Rheum Dis. 2011;70(6):935–42.

69. Salaffi F, Di Carlo M, Vojinovic J, Tincani A, Sulli A, Soldano S, et al. Validity of the rheumatoid arthritis impact of disease (RAID) score and definition of cut-off points for disease activity states in a population-based European cohort of patients with rheumatoid arthritis. Joint Bone Spine. 2018;85(3):317–22.

70. Dougados M, Brault Y, Logeart I, van der Heijde D, Gossec L, Kvien T. Defining cut-off values for disease activity states and improvement scores for patient-reported outcomes: the example of the Rheumatoid Arthritis Impact of Disease (RAID). Arthritis Res Ther. 2012;14(3):R129.

71. Mistry J, Sharif M, Prideaux A, Smith C, Sumbwanyambe M, Sibley M, et al. Use of rheumatoid arthritis impact of disease (RAID) in routine care; identification of DAS28 remission and unmet patient-reported outcomes. Rheumatol Adv Pract. 2020;4(2):rkaa013. https://doi.org/10.1093/rap/rkaa013.

72. Fautrel B, Morel J, Berthelot J-M, Constantin A, De Bandt M, Gaudin P, et al. Validation of FLARE-RA, a self-administered tool to detect recent or current rheumatoid arthritis flare. Arthritis Rheumatol. 2017;69(2):309–19.

73. Myasoedova E, De Thurah A, Erpelding M-L, Schneeberger EE, Maribo T, Citera G, et al. Definition and construct validation of clinically relevant cutoffs on the Flare Assessment in Rheumatoid Arthritis (FLARE-RA) questionnaire. Semin Arthritis Rheum. 2020;50(2):261–5.

74. de Thurah A, Maribo T, Stengaard-Pedersen K. Patient self-assessment of flare in rheumatoid arthritis: criterion and concurrent validity of the Flare instrument. Clin Rheumatol. 2016;35(2):467–71.

75. Thurah A, Stengaard-Pedersen K, Axelsen M, Fredberg U, Schougaard LMV, Hjollund NHI, et al. Tele-health followup strategy for tight control of disease activity in rheumatoid arthritis: results of a randomized controlled trial. Arthritis Care Res. 2018;70(3):353–60.

76. Knudsen LR, Thurah A, Lomborg K. Experiences with telehealth followup in patients with rheumatoid arthritis: a qualitative interview study. Arthritis Care Res. 2018;70(9):1366–72.

77. Ometto F, Raffeiner B, Bernardi L, Botsios C, Veronese N, Punzi L, et al. Self-reported flares are predictors of radiographic progression in rheumatoid arthritis patients in 28-joint disease activity score

remission: a 24-month observational study. Arthritis Res Ther. 2016;18(1):89.

78. Barton JL, Criswell LA, Kaiser R, Chen YH, Schillinger D. Systematic review and metaanalysis of patient self-report versus trained assessor joint counts in rheumatoid arthritis. J Rheumatol. 2009;36(12):2635–41.

79. Chaudhry SR, Thavaneswaran A, Chandran V, Gladman DD. Physician scores vs patient self-report of joint and skin manifestations in psoriatic arthritis. Rheumatology (Oxford). 2013;52(4): 705–11.

80. Yazdany J, Trupin L, Gansky SA, Dall'era M, Yelin EH, Criswell LA, et al. Brief index of lupus damage: a patient-reported measure of damage in systemic lupus erythematosus. Arthritis Care Res. 2011;63(8):1170–7.

81. Drenkard C, Yazdany J, Trupin L, Katz PP, Dunlop-Thomas C, Bao G, et al. Validity of a self-administered version of the brief index of lupus damage in a predominantly African American systemic lupus erythematosus cohort. Arthritis Care Res. 2014;66(6): 888–96.

82. Katz P, Trupin L, Rush S, Yazdany J. Longitudinal validation of the brief index of lupus damage. Arthritis Care Res. 2014;66(7):1057–62.

83. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol. 1994;21(12):2286–91.

84. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol. 1994;21(12):2281–5.

85. Doward LC, Spoorenberg A, Cook SA, Whalley D, Helliwell PS, Kay LJ, et al. Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. Ann Rheum Dis. 2003;62(1):20–6.

86. Pincus T, Summey JA, Soraci SA Jr, Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. Arthritis Rheumatol. 1983;26(11):1346–53.