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REVIEW

Clinical management of patients with rheumatoid arthritis during the COVID-19 pandemic

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) pandemic raises a great challenge in the management of patients with rheumatoid arthritis (RA), which are generally more susceptible to infection events because of the autoimmune condition itself and the treatment with immunomodulatory drugs. The use of disease-modifying anti-rheumatic drugs (DMARDs), including biologics and targeted-synthetic DMARDs, has aroused particular interest because of both their immunosuppressive effects and their hypothetical potential in COVID-19 treatment.

Areas covered: For this narrative review, a literature search was conducted between December 2019 and February 2021 on PubMed including epidemiological studies, gathering the main evidence available to date about the impact of COVID-19 on RA patients and the influence of anti-rheumatic drugs on patients' susceptibility to this infection. We also summarize the recommendations from the international guidelines on the management of rheumatic diseases and treatments in this pandemic context, especially focused on RA.

Expert opinion: About a year after the outbreak of the pandemic, we are able to answer some of the most relevant questions regarding patients with RA and their management in this pandemic context. Our efforts must now be directed toward consolidating the currently available data with more rigorous studies and facing new issues and challenges including, foremost, vaccination.

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Clinical management; coronavirus disease 2019; disease-modifying anti-rheumatic drugs (DMARDs); glucocorticoids; guidelines; immunosuppressive treatments; rheumatoid arthritis

1. Introduction

Since December 2019, when the novel coronavirus SARS-CoV -2 has been discovered in Wuhan in China, the pandemic of coronavirus disease 2019 (COVID-19) has spread globally, counting nowadays more than 121 million positive cases and almost 2.6 million deaths worldwide [1]. Although increasing progress has been made about the mechanisms underlying the disease, the pathogenesis of COVID-19 is not completely elucidated. What is known is that the major clinical manifestations and complications of the disease are related to cytokine dysregulation and a state of hyperinflammation, defined as cytokine storm, that can lead to acute respiratory distress syndrome (ARDS), multiorgan failure, and death [2]. The crucial role of immune response raised researchers and scientists interest in anti-rheumatic drugs, such as immunomodulators (e.g. hydroxychloroquine [HCQ], chloroquine [CQ]), anti-cytokines (such as interleukin [IL] 1, IL6, tumor necrosis factor [TNF], and granulocyte-macrophage colony-stimulating factor [GM-CSF]) and Janus kinase (JAK) inhibitors [3,4].

On the other hand, patients with rheumatic inflammatory disease, such as rheumatoid arthritis (RA), are known to be particularly susceptible to infections due to underlying immune system dysfunction and to chronic treatments with immunosuppressive medications [5–7]. With regards to the specific risk of SARS-CoV-2 infection, the available information from the literature (mostly provided by case series and survey-based designs), suggests that rheumatic patients are not at higher risk of developing COVID-19 than the general population, but they may have a higher likelihood of having complications, such as the need of mechanical ventilation [8,9]. Additionally, glucocorticoids exposure and increased prevalence of comorbidities (as cardiovascular diseases, obesity, diabetes mellitus, etc.) may further increase the risk of a worse prognosis [10].

Another clinical challenge is related to the potential atypical presentation of COVID-19 in patients on immunosuppressants. For example, glucocorticoids (GCs) and nonsteroidal anti-inflammatory drugs (NSAIDs) may inhibit a febrile response and IL-6 inhibitors prevent a rise in inflammatory markers [11]. Also, to be considered that symptoms like arthralgia, myalgia, fever, and elevation of inflammatory indexes, may be difficult to distinguish in RA patients between a disease flare and a SARS-CoV-2 infection. Conversely, the viral infection can lead to reactivation or a worsening of disease activity in RA patients.

Furthermore, patients with RA, along with patients with other autoimmune chronic arthritis, because of the highly disabling nature of the disease and the potential treatment toxicity, need to be strictly followed, thus requiring frequent

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Article highlights

- The incidence and the outcome of COVID-19 among patients with RA is consistent with that of a healthy population, but evidence suggests a higher risk of respiratory failure.
- Risk factors predicting poor outcome include age, comorbidity (such as cardiovascular, lung and renal chronic diseases), and treatment with rituximab or glucocorticoids.
- Rheumatologists' goal, even in this pandemic context, is to ensure adequate disease control and, contemporarily, to minimize the patient's risk of contagion.
- The treatment with c/ts/bDMARDs, while safely indicated in the absence of SARS-CoV-2 infection, should be discontinued in case of confirmed COVID-19, with the opportunity to discuss treatment changes on a case-by-case basis
- SARS-CoV-2 vaccination is opening a window of hope and an important field of research and investigation for rheumatic patients.

access to medical care for clinical assessment. These needs must adapt to the health emergency situation, in which it is preferable to minimize the exposure of the patients to the hospital environment and, thus, to potential SARS-CoV-2 contagion.

Therefore, it is crucial to provide patients and rheumatologists with clinical guidance in order to advise about how to treat and protect our patients at the best of our knowledge. In this review, we will analyze the available evidences about the impact of COVID-19 on RA patients and synthesize current recommendations from international guidelines or consensus documents on management of rheumatic diseases and treatments in this pandemic context, especially focused on RA. A literature search was conducted between December 2019 and February 2021 on PubMed including epidemiological studies (cohort and case-control studies, local and global registries, electronic health records), systematic literature reviews, national and international guidelines and recommendations. The search included the terms coronavirus 2019, COVID-19, rheumatoid arthritis, rheumatic diseases, immunosuppressive treatments, and biologic therapy. The results have been summarized in a narrative review.

2. COVID-19 in RA patients

2.1. Epidemiology, clinical course and outcomes

Is there an increased risk of COVID-19 infection in RA patients? Do RA patients have a worse clinical course or outcomes? Do they have an increased mortality rate?

In the last year, an impressive number of case series and reports have examined cases diagnosed with COVID-19 among patients with rheumatic diseases. These studies developed from the urgent need to answer a fundamental question, for both patients and rheumatologists, regarding the real risk of SARS-CoV-2 infection in rheumatic patients. At the same time, rheumatic population has attracted the attention of researchers and clinicians, since many of these patients are long-term users of drugs that have been identified as potential COVID-19 treatments, such as hydroxychloroquine or tocilizumab.

Almost all the epidemiological studies have been conducted on rheumatic patients, including all the immune-mediated inflammatory diseases (inflammatory arthritis, connective tissue diseases, vasculitis, etc.), while direct data on rheumatoid arthritis patients are lacking. According to these studies, the incidence of COVID-19 in rheumatic cohorts seems to be similar to the general population [12–14].

However, data from the COVID-19 Global Rheumatology Alliance (C19-GRA) Global Registry showed that, on 28 December 2020, the commonest rheumatic disease in which COVID-19 cases were documented was RA (1540 patients out of 3939) [15]. The same perception arises from other studies where the higher percentage of rheumatic patients in which COVID-19 has been documented have a diagnosis of RA [12,13,16–18]. Incidentally, rheumatoid arthritis is one of the most common diseases among rheumatology outpatients, so it is not known if the prevalence of RA patients among COVID-19 cases is due to an increased risk of infection or just a higher proportion among the study population. However, in a large German cohort, patients with spondyloarthritides showed a lower risk of hospitalization compared with RA (OR 0.46; 95%CI 0.23 to 0.91) [10].

Clinical course and outcomes of COVID-19 in rheumatic patients have also been investigated. The C19-GRA published report [19] found that 46% of the cases were hospitalized and 9% died. No information about ventilation outcomes was reported. The results of this study, based on physician-reported registries, may be affected by selection bias toward more severe cases, overestimating the severity of COVID-19 in the patient population, as asymptomatic patients or those with mild clinical course may not have been captured. A comparative cohort study conducted in Boston, MA, including data from electronic health records, examined differences in outcomes of COVID-19 in patients with and without rheumatic disease from a large healthcare system [20]. The two groups did not differ for symptoms and hospitalization (44% versus 42%) but those with rheumatic disease had a higher odds ratio (OR) for intensive care admission and mechanical ventilation (48% versus 18%, OR 3.11), even though mortality was comparable between the two groups (6% vs 4%). Notably, among patients with rheumatic disease, those hospitalized were older and had more comorbidities. Similar findings come from a retrospective study in Chinese patients from Wuhan [8] where the authors examined the clinical characteristics and outcomes of 21 patients with different rheumatic diseases from a sample of 2326 patients with COVID-19 who were hospitalized. Length of hospital stay and mortality rate were similar between rheumatic and non-rheumatic groups, while respiratory failure was more common in rheumatic cases (38% vs 10%, $p < 0.001$).

2.2. Risk factors associated with COVID-19 outcomes

Are there any specific risk factors in RA patients associated with COVID-19 outcomes?

Within the general population, it has been widely proven that risk factors predicting poor outcomes in COVID-19 patients include older age (>65 years) and comorbidities, such as obesity, hypertension, diabetes mellitus, chronic lung disease, chronic kidney disease (CKD), and cardiovascular disease (CVD) [21,22]. Similar findings emerged from studies on rheumatic patients: the higher odds of hospitalization were associated with age>65 years (OR 2.24; 95%CI 1.12 to 4.47), but even more>75 years (OR 3.94; 95%CI 1.86 to 8.32), CVD (OR 3.36; 95%CI 1.5 to 7.55), lung disease (OR 2.79; 95%CI 1.2 to 6.49), and chronic kidney disease (OR 2.96; 95%CI 1.16 to 7.5) [10].

2.3. Impact of anti-rheumatic therapy on COVID-19 incidence and severity

Do immunosuppressive/immunomodulatory anti-rheumatic drugs influence the risk of COVID-19 infection?

As mentioned, the role of immunosuppressive and immunomodulatory anti-rheumatic drugs in this pandemic context has raised many issues. Substantial attention has been given to some of these drugs (such as GCs, hydroxychloroquine, tocilizumab, baricitinib, adalimumab, canakinumab, and mavrilimumab) for their potential in the prevention and management of COVID-19 and associated inflammatory sequelae of infection [3]. Concurrently the exposure to some of these treatments, with particular regard to bDMARDs may be related to an increased risk of infections, in particular, bacterial and opportunistic infections [23,24]. The risk of acute viral respiratory events has been recently reviewed by Kilian et al. [25], who found that the exposure to JAK inhibitors, anti-TNF, and anti-IL17, but not to conventional synthetic DMARDs (csDMARDs) (as methotrexate, leflunomide, or sulfasalazine), may be associated with a higher frequency of mild viral respiratory infections, especially of the upper respiratory tract. However, their use was not associated with worse respiratory outcomes, including bronchitis and pneumonia, nor with complications such as hospitalization and mortality [25]. JAK inhibition has also been associated with an increased risk of herpes zoster reactivation [26], which seems to be related to the disruption of an adequate antiviral immune response mediated by type I and type II interferons [27]. Moreover, most studies conducted on GCs have shown an increased dose-dependent for both common and serious infections, especially in patients receiving medium to high GCs doses (more than 7.5 mg daily of prednisone equivalent) [28,29].

Concerning the specific risk of SARS-CoV-2 infection, little is known so far. Preliminary data come from different case series. In an Italian survey conducted on 955 patients (531 with RA) under treatment with biologic/targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs), the incidence of confirmed COVID-19 was consistent with the general population (0.62% vs 0.66%; p = 0.92) and none of the patients had severe complications or required intensive care treatment [30]. Another survey-based study conducted by our group in a cohort of 2050 patients with chronic inflammatory arthritis showed a decreased risk in b/tsDMARDs users (OR 0.47, 95% CI 0.46–0.48) while csDMARDs did not modify the odds of infection [31]. On a Spanish cohort of 123 patients with autoimmune inflammatory rheumatic disease and COVID-19, 54 patients required hospital admission related to COVID-19; patients exposed to DMARDs were not at higher risk of hospitalization, and those treated with anti-TNF had a statistically significant lower risk (OR 0.13, 95% CI 0.03–0.63) [32]. Likewise, in Ireland, it has been shown that the frequency of COVID-19 was lower in those on immunosuppressive medication (OR 0.48, 95% CI 0.27–0.88) [33]. A preliminary analysis on risk related to DMARDs exposure is also included in the C19-GRA study: compared with patients who were not receiving DMARDs, patients receiving bDMARDs (with TNF inhibitors being the most commonly prescribed) were less likely to be hospitalized (adjusted OR 0.46, 95% CI 0.22–0.93). Interpretation of these findings should be cautious. Because of the design of the studies, it is not possible to conclude if these observations could be attributable to a protective effect of bDMARDs or, instead, to a higher prevalence of risk factors (such as older age and multiple comorbidities) in patients not receiving DMARDs [34]. Moreover, patients receiving these treatments need strict follow up at rheumatology clinics and, therefore, it is easier to identify mild cases of viral infection.

On the other hand, data from a cohort of 820 patients with rheumatic diseases (47% with RA), showed that patients who tested positive for COVID-19 were more likely to be receiving treatment with rituximab (20% vs 8%, OR 2.28 (95% CI 1.24–-6.32), as well as treatment with GC in dosages>5 mg/day (OR 3.67; 95%CI 1.49 to 9.05) [35].

About GCs, there are several reports of a worse outcome of COVID-19 in patients chronically treated with GCs. Data from the aforementioned C19-GRA registry cihighlighted an increased risk of hospitalization for COVID-19 (OR 2.05, 95% CI 1.06–3.96) among patients with rheumatic diseases, including connective tissue diseases and vasculitis, receiving prednisone doses ≥10 mg/day [19]. Similarly, our data showed a risk of COVID-19 increased in chronic GCs users at dose >2.5 mg daily (OR 4.22, 95% CI 1.74–10.23) [31]. Finally, a comprehensive meta-analysis of 62 observational studies including 319,025 patients with autoimmune diseases from 15 countries showed that GCs use prior to COVID-19 significantly contributed to the disease prevalence; meanwhile, therapies including csDMARDs and b/tsDMARDs did not contribute to the risk of COVID-19. In terms of the clinical outcomes, subgroup analyses according to medical therapies showed that patients treated with GCs, csDMARDs or b/tsDMARDs–csDMARDs combination therapy had a 2–3 times higher rates of hospitalization, ICU admission, ventilation and death, whereas those treated with b/tsDMARDs monotherapy were associated with a lower risk of severe COVID-19, suggesting their safety in the COVID-19 pandemic [36].

2.4. COVID-19 pneumonia and RA-related interstitial lung disease (RA-ILD)

A variable proportion, ranging from 10 to 66%, of RA patients may develop interstitial lung disease (RA-ILD), mainly showing usual interstitial pneumonia (UIP) pattern, followed by a nonspecific interstitial pneumonia (NSIP) pattern, typically characterized by a chronic progression over years [37–39].

Acute exacerbation (AE) is a possible, critical, complication of RA-ILD, especially of the UIP pattern, which manifests histopathologically as diffuse alveolar damage (DAD) with an early edematous phase followed by hyaline membrane formation, desquamation of pneumocytes, and an increased interstitial mononuclear infiltrate. Radiologically, it shows diffuse, bilateral ground-glass opacification on high-resolution computed tomography (HRTC) [40]. Similar histological and radiological findings have been described in ARDS secondary to severe SARS-CoV-2 infection [41]. Pathogenesis of both ILD-AE and ARDS is poorly understood but both involve hyperinflammation, mainly driven by T helper 1 and M1 machrophages, characterized by secretion of proinflammatory cytokines, such as TNFα, IL-6, and IL-12, extracellular matrix destruction, and apoptosis [40,42]. Moreover, the excessive inflammatory response promotes an hypercoagulable state, directly, or indirectly through endothelial damage [43].

The existence of common pathogenic mechanisms represents a challenge for possible therapeutic options for both COVID-19 pneumonia and ILD. Among others, IL6 inhibitor, tocilizumab, is of particular interest for its ability to counter the SARS-CoV-2 induced-cytokine storm [44] and, on the other hand, its potential effect on the stabilization of lung involvement in patients with RA-ILD [45,46]. The role of tocilizumab for the treatment of ILD was recently validated in patients with systemic sclerosis (SSc) through a randomized, placebo-controlled, clinical trial in which patients treated with tocilizumab showed a lower rate of progressive loss of lung function compared to placebo [47]. These results led to the FDA approval of tocilizumab for the treatment of SSc-ILD.

Some authors also suggest the inhibition of toll-like receptor 4 (TLR4) [48], which have been previously investigated as a possible therapeutic target for preventing lethal complications of some viral diseases [48]. The role of TLR4 in the pathogenesis of RA and RA-ILD has been demonstrated and its inhibition in experimental model showed to suppress the production of IL6, IL8, metalloproteinase-1 and vascular endothelial growth factor [49]. However, an anti-TLR4 monoclonal antibody has been tested for the treatment of anti-citrullinated protein antibodies (ACPA)-positive RA patients but failed in demonstrating its efficacy [50].

In this pandemic context, patients with COVID-19 and pre-existing ILD, idiopathic or related to RA or CTDs, compared to control group with COVID-19 without ILD, showed to be at higher risk to be admitted to the hospital (74% vs. 58%) and to require ICU care (47% vs. 23%), and to have a higher mortality rate (33% vs. 13%) [51]. Drake and colleagues examined mortality among 161 patients with ILD hospitalized with COVID-19 and compared it with a matched control group of patients with COVID-19 without underlying lung disease [52]. They found that patients with ILD have significantly higher in-hospital mortality compared with those without ILD (49% vs. 35%). Patient with idiopathic ILD (namely idiopathic pulmonary fibrosis [IPF]) had the poorer survival rate compared to non-IPF patients (HR, 1.74; 95% CI, 1.16–2.60; p 0.007 vs. HR, 1.50; 95% CI, 1.02–2.21; p 0.040). Among patients with non-IPF, those with chronic hypersensitivity pneumonitis and RA-ILD had the highest mortality rate (50% [7/14] and 40% [4/10], respectively) [52], Authors have hypothesized that the proportion of mortality rate and the presence of factors associated with poor prognosis (poor lung function before admission, fibrotic pattern of ILD) are consistent with an AE of ILD induced by respiratory virus infection.

3. Managing RA during COVID-19 pandemic

The most authoritative organizations in the rheumatology field, namely the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), have readily provided recommendations and guidance statements to help rheumatologists in these difficult and uncertain pandemic contexts [53,54]. The authors emphasize that these documents, due to the rapidly expanding information and evolving evidence related to COVID-19, are provisional and may be subject to changes over time. Here we summarize the present recommendations and discuss their implications in clinical practice (Table 1).

3.1. Preventive and control measures

General public health measures to mitigate infection risk of COVID-19 have been widely spread by the World Health

Table 1. Key recommendation for clinical management of patients with RA during the COVID-19 pandemic.

General recommendations	
Patients must adhere to general preventive measures prescribed by the health authorities in their country, such as hand hygiene, social distancing, and wearing a mask in public, among others.	
When possible, health care encounters should be reduced, while use of telemedicine should be encouraged.	
Following SARS-CoV-2 infection or exposure, patients should promptly alert their rheumatologists who will provide the most appropriate guidance on a case-by-case basis.	
Management of anti-rheumatic treatments	
GCs	Patients who are chronically treated with GCs should continue their treatment at the lowest effective dose, even in case of SARS-CoV-2 infection. Avoid abrupt withdrawal.
NSAIDs	Can be continued unless the patient presents with severe manifestations of COVID-19 such as kidney, cardiac, or gastrointestinal injury.
Antimalarials (HCQ/CQ)	Can be continued. In case of definite or suspected SARS-CoV-2 infection, consider suspension in case of chronic heart failure and/or association with azithromycin.
csDMARDs	Can be continued. Recommended suspension of SSZ, MTX, LFN, in case of definite or suspected SARS-CoV-2 infection
bDMARDs	Can be continued. Recommended suspension in case of definite or suspected SARS-CoV-2 infection. Even if, according to ACR guidance, anti-IL6 receptor inhibitors could be continued in selected circumstances of active COVID-19, we suggest a more cautious approach pending better definition of these circumstances and more consistent data on anti-IL6 efficacy in COVID-19.
tsDMARDs	Can be continued. Recommended suspension in case of definite or suspected SARS-CoV-2 infection.
Vaccination	Seasonal and influenza vaccinations are recommended. SARS-CoV-2 vaccination is recommended.

ACR, American College of Rheumatology; bDMARDs, biologic disease-modifying anti-rheumatic drugs; cDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; COVID-19, Coronavirus disease 2019; CQ, chloroquine; GCs, glucocorticoids; HCQ, hydroxychloroquine; LFN, leflunomide; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; SSZ, sulfasalazine; tsDMARDs, targeted synthetic disease-modifying anti-rheumatic drugs.

Organization (WHO) [55] and other public health agencies. These precautions are of paramount importance even for patients with RA, who are strongly advised to comply with all preventive and control measures prescribed by the health authorities in their country. Such measures include optimal hand hygiene, social distancing, and wearing a mask in public, among others. To date, since there is no reason to assume that RA patients carry a higher (or lower) risk of being infected, they should not take any different measures than those issued for the general population.

3.2. Management of anti-rheumatic treatments

According to current knowledge, there is no established association between a specific anti-rheumatic treatment and the likelihood (increase, decrease, or no change in the risk) of developing COVID-19. Conversely, it has been ascertained that poor control of disease activity correlates with an increased risk of acquiring infections. In particular, RA patients with moderate to high disease activity as compared with patients with low disease activity and those in remission show an increase in incidence of serious infections [56]. Data from the CORRONA (Consortium of Rheumatology Researchers of North America) registry have shown that each 0.6 unit increase in Disease Activity Score on 28 joints (DAS28) score corresponds to a 4% increased rate of outpatient infections and a 25% increased rate of infections requiring hospitalization [57]. Moreover, flares of the disease may require the introduction, or increased dose, of GCs that, as previously discussed, are an established risk factor for COVID-19; patients with high or moderate disease activity may also necessitate being physically evaluated at the outpatient clinic, thus exposing themselves to potential sources of contagion. Recently, moderate or high disease activity have been associated with a higher odds of COVID-19 hospitalization among patients with rheumatic and musculoskeletal disease [10].

In view of the above, both ACR and EULAR agree that patients with RA who do not have suspected or confirmed COVID-19 should be advised to continue their treatment unchanged, namely NSAIDs, GCs, cs/ts/bDMARDs, osteoporosis medications, and analgesics, among others.

Glucocorticoids (GCs). The role of glucocorticoids during COVID-19 infection is highly controversial. Initial studies performed on their use in COVID-19 were not satisfactory, and in some cases adverse effects predominated on benefits [58–60]. More recently, encouraging data are emerging that demonstrate that the immunosuppressive effects of GCs could mitigate the hyperinflammation during the late phases of infection, reducing mortality and length of hospitalization [61,62]. Indeed, GCs are now strongly recommended according to WHO guidelines for the treatment of patients with severe and critical COVID-19 [63]. Regarding RA clinical management, patients who are chronically treated with GCs should continue their treatment, according to the well-known good clinical practice of the 'lowest possible dose' [64], even in case a patient manifests symptoms of COVID-19. The abrupt withdrawal of GCs treatment should be avoided because of the possibility of hypothalamic–pituitary–adrenal axis suppression [65], which could be particularly critical in case of stressful events, such as a viral infection.

NSAIDs. Despite there has been conflicting advice regarding NSAID use in patients with COVID-19, currently there is no evidence in favor or against the use of NSAIDs in COVID-19 [66,67]. According to the EULAR taskforce NSAIDs could be used without additional risk requiring no specific recommendation [53]; ACR guidelines suggest that the use and prescription of NSAIDs can be continued unless the patient presents with severe manifestations of COVID-19, such as kidney, cardiac, or gastrointestinal injury. In the absence of severe respiratory symptoms, the panel demonstrated low consensus with regard to stopping NSAIDs [54].

Conventional synthetic DMARDs. In vitro studies with HCQ and CQ have demonstrated their antiviral capacity [68], stimulating several clinical trials to verify their efficacy in treatment, prevention and post-exposure prophylaxis. The results so far have been controversial [69] with no clear evidence of efficacy, leading WHO panelists to recommend against the use of HCQ or CQ for the treatment of COVID-19 patients [63]. Case series on rheumatic patients have shown that those who chronically use HCQ have the same incidence of SARS-CoV-2 infections compared to those who do not use HCQ [12,70]. Nonetheless, HCQ and CQ are relatively safe drugs and their use is not contraindicated in this pandemic context, in the absence of infection or known SARS-CoV-2 exposure. Attention must be paid in the case of active or presumptive COVID-19 since an increase of mortality related to cardiotoxicity (QT prolongation and arrhythmias), especially among hospitalized patients receiving other QT-prolonging agents (such as azithromycin), have been observed [71]. ACR's task force have recently reviewed the recommendation on HCQ/CQ, suggesting to temporarily withhold HCQ/CQ following SARS–CoV-2 exposure or infection [54]. Intake of other csDMARDs, such as sulfasalazine (SSZ), methotrexate (MTX), and leflunomide (LFN), while safely continued in the absence of known SARS–CoV-2 exposure, should be temporarily suspended in the setting of active infection. EULAR taskforce suggests the opportunity, in case of infection with mild symptoms, to discuss treatment changes with DMARDs on a case-by-case basis.

Biologics and targeted synthetic DMARDs. As for csDMARDs, in patients with stable disease with no symptoms or suspicion of COVID-19, ACR and EULAR's taskforces recommend to continue the treatment with bDMARDs or tsDMARDs. In addition, during the pandemic there is no contraindication to start these treatments in case of csDMARDs failure, despite some uncertainty from the ACR panel regarding JAKis safety in this context. Indeed, despite baricitinib have been suggested to mitigate COVID-19 impact by interfering with cellular entry of SARS-CoV-2 and by mitigating inflammatory response [72], it also suppresses a crucial innate antiviral pathway as demonstrated by its association with HZ reactivation [73], raising some concerns on its safe use in this setting [74]. In case of documented or suspected SARS-CoV-2 infection, regardless of COVID-19 severity, it is recommended to temporarily stop b/tsDMARDs, with the exception, according to ACR's panel, of anti-IL6 receptor inhibitors that, in selected circumstances, could be continued. This statement derives from the therapeutic success of tocilizumab observed in different cohort

studies on patients with COVID-19 with severe/critical respiratory involvement, which showed a marked clinical improvement in association to tocilizumab administration [75–77]. Enthusiasm regarding the use of this drug then quickly dissipated for the incoming results of subsequent randomized control studies that showed no clear benefits with the use of tocilizumab in COVID-19 [78,79]. In light of these insights, while waiting for more consistent data, it might be safer to extend the recommendation of stopping bDMARDs even to IL6 inhibitors.

3.3. Management of patients follow-up

The mainstay for optimal management of patients with RA is the treat-to-target strategy, based on frequent clinical assessment to evaluate disease activity and patient's general conditions, in order to promote a good control of disease and a good quality of life [80]. In this pandemic context, tight control of RA patients remains crucial, although it has to balance with the issue of protecting patients and preventing SARS-CoV-2 infection. For these reasons, as also suggested by recommendations, efforts should be made to implement strategies to reduce health care encounters, for example, facilitating the use of telemedicine. Patients whose disease and drug treatment are stable, can be suggested to postpone the visit once or twice, ensuring a prompt remote consultation in case of need. In cases where the visit, or the intravenous therapy, cannot be deferred (as in patients with active disease or who have recently started or changed the therapy, or with signs of drug toxicity), every precaution necessary to prevent virus spread must be taken, including social distancing (when possible), use of appropriate personal protective equipment, reduction of permanence stay in the hospital, limiting the entrance of relatives.

During the COVID-19 lockdown, the implementation of telemedicine has dramatically increased and has proven to be feasible and effective for the online management of patients with rheumatoid arthritis and psoriatic arthritis [81,82], as well as for the assessment of COVID-19 infection in a cohort of patients with systemic lupus erythematosus [83]. Since it is not possible to predict how long this period of restrictions will last, it is advisable that each referral center soon develop a flexible telehealth system to provide good-quality healthcare assistance and continuity of care for rheumatic patients.

3.4. Vaccination

Patients with RA should be advised to vaccinate against influenza and pneumococci. This recommendation is already part of good clinical practice [84]. However, the EULAR taskforce strengthens this statement since infection by influenza or pneumococcus could create clinical confusion with COVID-19 [53].

Concerning vaccination against SARS-CoV-2, currently, there are three main types of COVID-19 vaccines, acting with different mechanisms of action: mRNA vaccines, vector vaccines, and protein subunit vaccines. To date, no evidence exists on the safety and efficacy of the new vaccines in patients with rheumatic diseases. Data on the commonest vaccinations suggest that vaccines in RA patients are efficacious, safe (except for live-attenuated vaccines in immunosuppressed patients), and generally immunogenic [85]. In relation to anti-rheumatic treatments, most of the studies demonstrated similar rates of immunogenicity among patients receiving c/b/tsDMARDs and healthy controls (HC), except for the studies in patients treated with rituximab, whose responses were severely impaired [85]: B cell depleting therapy has been associated with hampered antibody responses following influenza and pneumococcal vaccination [86,87]. In the absence of specific information about the performance of the emerging vaccines to COVID-19 in patients with RA, both EULAR and ACR have expressed their favorable opinion, suggesting that there are no reasons to withhold these vaccines from patients with rheumatic disease, even those receiving immunosuppressive treatments [88,89]. For those who are in treatment with rituximab, there is a significant plausible risk that anti-CD20 therapies may reduce the efficacy of a vaccine against SARS-CoV-2 [90]. Consistently with 2019 EULAR recommendations for vaccination, it is advisable to provide the vaccine at least 6 months after the administration and 4 weeks before the next course of B cell-depleting therapy [84], in order to allow memory and naive B cell repopulation and the potential to generate new antibody responses [91].

4. Conclusion

COVID-19 has forced important challenges to the entire scientific community, encouraging immense research efforts to face the pandemic. In the rheumatology field, one of the biggest challenges was the management of patients with RA who seem to be particularly vulnerable in this context due to the autoimmune condition itself and to the use of drugs potentially impairing the immune system. Based on data from observational studies published so far, the incidence and severity of SARS-CoV-2 infection in RA patients do not differ from those observed in the general population. At the same time, immunosuppressive/immunomodulating therapies appear not to be associated with an increased risk of infection or life-threatening complications. Therefore, non-infected patients can safely continue all DMARDs with the indication to temporarily suspend the treatment in case of virus contagion. Rheumatologists should always be consulted to implement the best treatment strategy on a case-by-case basis through a proper risk-benefit analysis. Placing trust and optimism in the arrival of new vaccines, patients must be encouraged to adopt every preventive measure to contrast virus spread.

5. Expert opinion

At the onset of the pandemic, the healthcare community was found unprepared to face an unknown and initially underestimated enemy. If, on the one hand, it was immediately urgent to face a medical emergency requiring a complete reorganization of health resources, on the other hand, the need has emerged to identify and adequately manage the most critical patients, such as those suffering from chronic

diseases. Nearly a year later, the efforts and collaboration implemented have significantly improved our knowledge and ability to cope with COVID-19. The data available from several epidemiological studies that have addressed this issue have clarified that RA, although treated with potentially immunosuppressive drugs, does not represent an additional risk factor for acquiring SARS-CoV-2 infection. This means that chronic therapy with csDMARDs (such as HCQ, MTX, leflunomide, sulfasalazine), tsDMARDs (such as JAK inhibitors) or bDMARDs (such as anti-TNF, anti-IL6, anti-CD20, abatacept) can be considered overall safe even during the pandemic and indeed its maintenance should be recommended in order to reduce the incidence of RA flares, which, on the contrary, increase the risk of infection also due to the use of higher doses of GCs in these cases. However, some therapeutic options deserve special consideration. Rituximab (RTX) is a monoclonal antibody inducing B cell depletion, known to be associated with an increased risk of serious infections [92]. In relation to SARS-CoV-2, a higher risk of hospitalization has been reported in rheumatic patients with COVID-19 chronically treated with rituximab [35,93]. This finding should not be considered an absolute contraindication to drug maintenance during the pandemic, but RT users should be monitored even more closely for early detection of signs and symptoms of possible infection.

Among the bDMARDs used in rheumatology, IL-6 inhibitors have found the greatest application as a potential therapy for COVID-19. The rationale behind this use lies in the theoretical ability of tocilizumab and sarilumab to counteract the hyperinflammatory reaction that characterizes the more severe forms of SARS-CoV-2 interstitial pneumonia, which affect a clear minority of patients. Data are still conflicting, and a reduction in mortality associated with tocilizumab has been reported only in observational studies (but not confirmed in RCTs), limited to subjects with high levels of C-reactive protein (CRP) [94] or D-dimer [95]. In our opinion, these results should not lead to prefer IL-6 inhibitors to other bDMARDs as a therapy for RA in the pandemic era, since their protective effect on the onset of more severe patterns of COVID-19 has never been demonstrated so far. Of interest, no higher risk of concomitant infections has been observed in hospitalized COVID-19 patients treated with tocilizumab [96].

Another issue that remains highly controversial is the role of antimalarial drugs as a possible treatment for COVID-19. After an initial phase of extensive use of chloroquine and hydroxychloroquine as preventive therapy of SARS-CoV-2 infection, the most recent data seem to discourage their prescription due to a general low efficacy and some important concerns about their safety profile [97]. Especially when used in combination with azithromycin, antimalarials have been associated with a high risk of QTc prolongation and increased mortality from cardiovascular events [98], which is why the ACR has recently recommended their discontinuation in case of SARS-CoV-2 infection [54]. These findings have also cast a shadow over chronic antimalarial therapy, which has been considered one of the safest in rheumatic patients for decades. It should be emphasized that the posology of hydroxychloroquine as therapy for mild forms of RA (200–400 mg daily) is significantly lower than that adopted in the treatment of COVID-19 (800–1200 mg daily). The data on this aspect are still not conclusive. Two literature reviews published in 2018 showed an overall low incidence of cardiologic complications (especially conduction disorders) induced by long-term use of antimalarials [99,100]. However, the most recent evidence coming from a retrospective analysis conducted on 14 claim databases from different countries, showed an increased risk of cardiovascular mortality (calibrated HR 1.65 [95% CI 1.12–2.44]) in long-term hydroxychloroquine users (n = 956 374) compared with a control group receiving sulfasalazine (n = 310 350) [101]. The clear limitations in the study design (e.g. heterogeneous populations, retrospective design, the use of sulfasalazine as comparative group) and the lack of RCTs conducted on this topic preclude drawing definitive conclusions, but still suggest a special caution in the maintenance of antimalarials in rheumatic patients experiencing COVID-19, especially in those with a previous history of chronic heart disease.

Beyond the progress made in the first 12 months of the pandemic, several issues still remain unresolved. Epidemiological data available so far are based on surveys or registries collecting COVID-19 confirmed cases only, namely patients who received a definite diagnosis according to a RT-PCR diagnostic test. Although these findings may provide a good picture of symptomatic COVID-19, available epidemiologic data lack information regarding asymptomatic/paucisymptomatic cases, which seem to account for the vast majority of SARS-CoV-2 infections according to preliminary results of seroprevalence studies conducted in the general population [102–105]. In this scenario, observational studies aimed at analyzing anti-SARS-CoV-2 antibody levels in rheumatic patients will play a crucial role in truly elucidating the role of autoimmune diseases and ongoing immunomodulatory therapies on the immune response to the virus. This information gains even more importance in light of the current vaccine schedule, which represents the greatest challenge in fighting COVID-19. Data on the efficacy and safety of the available vaccines in the general population are reassuring, as evidenced by both clinical trials [106–108] and observational real-life studies [109], but little is known about their effects in rheumatic patients. In the BNT162b2 mRNA Covid-19 vaccine phase III trial only 118 (0.3%) of 37,706 patients enrolled had a rheumatic disease. Although they were equally randomized (62 vs 56) to receive vaccine or placebo, no specific subanalysis was conducted in this group [106]. In the absence of evidence, according to EULAR and ACR positioning, it is reasonable to extend the current recommendation about vaccination even to vaccines against SARS-CoV-2. In this scenario, the coming months will be crucial to increase our knowledge through studies focused on the efficacy and safety of the available vaccines in patients with RA and other autoimmune diseases, with the aim of understanding how best to manage chronic therapy with immunomodulatory drugs in relation to vaccine

administration. In particular, it will be essential to evaluate the response to the vaccine in subjects undergoing therapy with drugs, such as methotrexate and rituximab, which have already been proven to reduce immunogenicity following influenza and pneumococcal vaccination [85,110,111].

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. WHO coronavirus (COVID-19) dashboard [Internet]. [2021 Mar 20]. Available from: https://covid19.who.int.
2. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. Travel Med Infect Dis. 2020;34:101623.
3. Rizk JG, Kalantar-Zadeh K, Mehra MR, et al. Pharmaco-Immunomodulatory Therapy in COVID-19. Drugs. 2020;80 (13):1267–1292.
4. Favalli EG, Ingegnoli F, De Lucia O, et al. COVID-19 infection and rheumatoid arthritis: faraway, so close! Autoimmun Rev. 2020;19 (102523):102523.
5. Doran MF, Crowson CS, Pond GR, et al. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum. 2002;46(9):2287–2293.
6. Mehta B, Pedro S, Ozen G, et al. Serious infection risk in rheumatoid arthritis compared with non-inflammatory rheumatic and musculoskeletal diseases: a US national cohort study. RMD Open. 2019;5 (1):e000935.
7. Caporali R, Caprioli M, Bobbio-Pallavicini F, et al. DMARDS and infections in rheumatoid arthritis. Autoimmun Rev. 2008;8 (2):139–143.
8. Ye C, Cai S, Shen G, et al. Clinical features of rheumatic patients infected with COVID-19 in Wuhan, China. Ann Rheum Dis. 2020;79 (8):1007–1013.
9. Cheng C, Li C, Zhao T, et al. COVID-19 with rheumatic diseases: a report of 5 cases. Clin Rheumatol. 2020;39(7):2025–2029.
10. Hasseli R, Mueller-Ladner U, Hoyer BF, et al. Older age, comorbidity, glucocorticoid use and disease activity are risk factors for COVID-19 hospitalisation in patients with inflammatory rheumatic and musculoskeletal diseases. RMD Open. 2021;7(1):e001464.
11. Favalli EG. Understanding the role of interleukin-6 (IL-6) in the joint and beyond: a comprehensive review of IL-6 inhibition for the management of rheumatoid arthritis. Rheumatol Ther. 2020;7 (3):473–516.
12. Favalli EG, Ingegnoli F, Cimaz R, et al. What is the true incidence of COVID-19 in patients with rheumatic diseases? Ann Rheum Dis. 2020. cited 2020 Dec 28. Available from: https://ard.bmj.com/content/early/2020/05/22/annrheumdis-2020-217615
13. Sarzi-Puttini P, Marotto D, Caporali R, et al. Prevalence of COVID infections in a population of rheumatic patients from Lombardy and Marche treated with biological drugs or small molecules: a multicentre retrospective study. J Autoimmun. 2020. 2020 Oct 20. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7506330/
14. Favalli EG, Agape E, Caporali R. Incidence and Clinical Course of COVID-19 in patients with connective tissue diseases: a descriptive observational analysis. J Rheumatol. 2020;47(8):1296.
15. The COVID-19 global rheumatology alliance global registry. [Internet]. [2020 Dec 28]. Available from: https://rheum-covid.org/updates/combined-data.html.
• **Global registry collecting information pertinent to COVID19 infection in patients with rheumatologic disease worldwide.**
16. Fredi M, Cavazzana I, Moschetti L, et al. COVID-19 in patients with rheumatic diseases in northern Italy: a single-centre observational and case–control study. Lancet Rheumatol. 2020;2(9): e549–e556.
17. Haberman R, Axelrad J, Chen A, et al. Covid-19 in immune-mediated inflammatory diseases—Case series from New York. N Engl J Med. 2020;383(1):85–88.
18. Scirè CA, Carrara G, Zanetti A, et al. COVID-19 in rheumatic diseases in Italy: first results from the Italian registry of the Italian Society for Rheumatology (CONTROL-19). Clin Exp Rheumatol. 2020;38 (4):748–753.
19. Gianfrancesco M, Hyrich KL, Al-Adely S, 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. 79(7): 859–866. 2020.
• **Preliminary data from the Global Registry.**
20. D'Silva KM, Serling-Boyd N, Wallwork R, 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):1156–1162.
21. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934–943.
22. Zhou F, Yu T, Du R, 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):1054–1062.
23. Rutherford AI, Subesinghe S, Hyrich KL, et al. Serious infection across biologic-treated patients with rheumatoid arthritis: results from the British society for rheumatology biologics register for rheumatoid arthritis. Ann Rheum Dis. 2018;77(6):905–910.
24. Barrett O, Abramovich E, Dreiher J, et al. Short- and long-term mortality due to sepsis in patients with rheumatoid arthritis. Rheumatol Int. 2017;37(6):1021–1026.
25. Kilian A, Chock YP, Huang IJ, et al., Acute respiratory viral adverse events during use of antirheumatic disease therapies: a scoping review. Semin Arthritis Rheum. 50(5): 1191–1201. 2020.
• **An updated review on frequency and severity of acute respiratory viral adverse events related to antirheumatic disease therapies.**
26. Bechman K, Subesinghe S, Norton S, et al. A systematic review and meta-analysis of infection risk with small molecule JAK inhibitors in

rheumatoid arthritis. Rheumatology (Oxford). 2019;58(10):1755–1766.
27. Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nat Rev Rheumatol. 2017;13(4):234–243.
28. Youssef J, Novosad S, Winthrop K. Infection Risk and Safety of Corticosteroid Use. Rheum Dis Clin North Am. 2016;42(1):157–176.
29. Fardet L, Petersen I, Nazareth I. Common infections in patients prescribed systemic glucocorticoids in primary care: a population-based cohort study. PLoS Med. 2016;13(5):e1002024.
30. Favalli EG, Monti S, Ingegnoli F, et al. Incidence of COVID-19 in patients with rheumatic diseases treated with targeted immunosuppressive drugs: what can we learn from observational data? Arthritis Rheum. 2020;72(10):1600–1606.
31. Favalli EG, Bugatti S, Klersy C, et al., Impact of corticosteroids and immunosuppressive therapies on symptomatic SARS-CoV-2 infection in a large cohort of patients with chronic inflammatory arthritis. Arthritis Res Ther. 22(1): 290. 2020.
• **A large cohort study that investigate the impact of glucocorticoids and immunosuppressive agents on COVID-19 in patients with chronic immune-mediated inflammatory arthritis.**
32. Ddf N, Leon L, Mucientes A, et al. Risk factors for hospital admissions related to COVID-19 in patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2020;79(11):1393–1399.
33. Murray K, Quinn S, Turk M, et al. COVID-19 and rheumatic musculoskeletal disease patients: infection rates, attitudes and medication adherence in an Irish population. Rheumatology. 2020. cited 2020 Dec 30. Available from: https://doi.org/10.1093/rheumatology/keaa694
34. Bengtsson K, Jacobsson LTH, Rydberg B, et al. Comparisons between comorbid conditions and health care consumption in rheumatoid arthritis patients with or without biological disease-modifying anti-rheumatic drugs: a register-based study. BMC Musculoskelet Disord. 2016;17(1):499.
35. Santos CS, Férnandez XC, Moriano Morales C, et al., Biological agents for rheumatic diseases in the outbreak of COVID-19: friend or foe? RMD Open. 7(1): e001439. 2021.
• **A retrospective observational study that assess the influence of bDMARDs on the COVID-19 infection rate and the prognosis of patients with rheumatic diseases.**
36. Akiyama S, Hamdeh S, Micic D, et al. Prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases: a systematic review and meta-analysis. Ann Rheum Dis. 2021;80(3):384–391.
37. Cassone G, Manfredi A, Vacchi C, et al. Treatment of rheumatoid arthritis-associated interstitial lung disease: lights and shadows. J Clin Med. 2020;9(4):1082.
38. Raimundo K, Solomon JJ, Olson AL, et al. Rheumatoid arthritis-interstitial lung disease in the United States: prevalence, incidence, and healthcare costs and mortality. J Rheumatol. 2019;46(4):360–369.
39. Hyldgaard C, Hilberg O, Pedersen AB, et al. A population-based cohort study of rheumatoid arthritis-associated interstitial lung disease: comorbidity and mortality. Ann Rheum Dis. 2017;76(10):1700–1706.
40. Leuschner G, Behr J. Acute exacerbation in interstitial lung disease. Front Med (Lausanne). 2017;4:176.
41. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4):420–422.
42. Huppert LA, Matthay MA, Ware LB. Pathogenesis of acute respiratory distress syndrome. Semin Respir Crit Care Med. 2019;40(1):31–39.
43. Vassiliou AG, Kotanidou A, Dimopoulou I, et al. Endothelial damage in acute respiratory distress syndrome. Int J Mol Sci. 2020;21. cited 2021 Mar 19. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7699909/
44. McGonagle D, Sharif K, O'Regan A, et al. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev. 2020;19(6):102537.
45. Manfredi A, Cassone G, Furini F, et al. Tocilizumab therapy in rheumatoid arthritis with interstitial lung disease: a multicentre retrospective study. Intern Med J. 2020;50(9):1085–1090.
46. Otsuji N, Sugiyama K, Arifuku H, et al. Effect of tocilizumab on interstitial lung disease (ILD) in patients with rheumatoid arthritis (RA). Eur Resp J. 2020;56. cited 2021 Mar 20. Available from: https://erj.ersjournals.com/content/56/suppl_64/747
47. Roofeh D, Lin CJF, Goldin J, et al. Tocilizumab prevents progression of early systemic sclerosis associated interstitial lung disease. Arthritis Rheum. cited 2021 Mar 19;n/a. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/art.41668
48. Manfredi A, Luppi F, Cassone G, et al. Pathogenesis and treatment of idiopathic and rheumatoid arthritis-related interstitial pneumonia. The possible lesson from COVID-19 pneumonia. Expert Rev Clin. 2020;16(8):751–770.
49. Samarpita S, Kim JY, Rasool MK, et al. Investigation of toll-like receptor (TLR) 4 inhibitor TAK-242 as a new potential anti-rheumatoid arthritis drug. Arthritis Res Ther. 2020;22(1):16.
50. Monnet E, Choy EH, McInnes I, et al. Efficacy and safety of NI-0101, an anti-toll-like receptor 4 monoclonal antibody, in patients with rheumatoid arthritis after inadequate response to methotrexate: a phase II study. Ann Rheum Dis. 2020;79(3):316–323.
51. Esposito AJ, Menon AA, Ghosh AJ, et al. Increased odds of death for patients with interstitial lung disease and COVID-19: a case-control study. Am J Respir Crit Care Med. 2020;202(12):1710–1713.
52. Drake TM, Docherty AB, Harrison EM, et al. Outcome of hospitalization for COVID-19 in patients with interstitial lung disease. An international multicenter study. Am J Respir Crit Care Med. 2020;202(12):1656–1665.
53. Landewé RB, Machado PM, Kroon F, 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):851–858.
54. Mikuls TR, Johnson SR, Fraenkel L, et al. American college of rheumatology guidance for the management of rheumatic disease in adult patients during the COVID-19 pandemic: version 3. Arthritis Rheum. 2021;73:e1–e12.
55. Advice for the public on COVID-19 – World Health Organization [Internet]. [cited 2020 Dec 31]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public.
56. Accortt NA, Lesperance T, Liu M, et al. Impact of sustained remission on the risk of serious infection in patients with rheumatoid arthritis. Arthritis Care Res. 2018;70(5):679–684.
57. Au K, Reed G, Curtis JR, et al. High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. Ann Rheum Dis. 2011;70(5):785–791.
58. Zha L, Li S, Pan L, et al. Corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19). Med J Aust. 2020;212(9):416–420.
59. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020;395(10223):473–475.
60. Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. Clin Immunol. 2020;214:108393.
61. RECOVERY Collaborative Group, HorbyP,et al. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. N Engl J Med. 2020.
• **Preliminary results from the RECOVERY trial showing the efficacy of dexamethasone in reducing mortality in patients hospitalized with COVID-19 who were receiving either invasive mechanical ventilation or oxygen alone.**
62. Siemieniuk RA, Bartoszko JJ, Ge L, et al. Drug treatments for COVID-19: living systematic review and network meta-analysis. BMJ. 2020;370:m2980.

63. Siemieniuk R, Rochwerg B, Agoritsas T, et al. A living WHO guideline on drugs for covid-19. BMJ. 2020;370:m3379.
64. Smolen JS, Rbm L, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020;79(6):685–699.
65. Mikuls TR, Johnson SR, Fraenkel L, 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):1241–1251.
66. The use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with COVID-19 [Internet]. [cited 2020 Dec 31]. Available from: https://www.who.int/news-room/commentaries/detail/the-use-of-non-steroidal-anti-inflammatory-drugs-(nsaids)-in-patients-with-covid-19.
67. Zhao D, Zhang S, Igawa T, et al. Use of nonsteroidal anti-inflammatory drugs for COVID-19 infection: adjunct therapy? Cardiol Rev. 2020;28(6):303–307.
68. Fantini J, Di Scala C, Chahinian H, et al. Structural and molecular modelling studies reveal a new mechanism of action of chloroquine and hydroxychloroquine against SARS-CoV-2 infection. Int J Antimicrob Agents. 2020;55(5):105960.
69. De Barros CM, Almeida Ca De F, Pereira B, et al. COVID-19 pandemic - A narrative review of the potential roles of chloroquine and hydroxychloroquine. Pain Physician. 2020;23(4S): S351–S366.
70. Favalli EG, Lucia OD, Biggioggero M, et al. Role of antimalarials in COVID-19: observational data from a cohort of rheumatic patients. Ann Rheum Dis. 2020 cited 2021 Jan 28; 218068. Available from: https://ard.bmj.com/content/early/2020/06/18/annrheumdis-2020-218068
71. Jankelson L, Karam G, Becker ML, et al. QT prolongation, torsades de pointes, and sudden death with short courses of chloroquine or hydroxychloroquine as used in COVID-19: a systematic review. Heart Rhythm. 2020;17(9):1472–1479.
72. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet. 2020;395 (10223):e30–e31.
73. Taylor PC, Keystone EC, Van Der Heijde D, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med. 2017;376(7):652–662.
74. Favalli EG, Biggioggero M, Maioli G, et al. Baricitinib for COVID-19: a suitable treatment? Lancet Infect Dis. 2020;20(9):1012–1013.
75. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci USA. 2020;117 (20):10970–10975.
76. Biran N, Ip A, Ahn J, et al. Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study. Lancet Rheumatol. cited 2020 Sep 15. 2020;2(10):e603-e612. Available from.
77. Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. Lancet Rheumatol. 2020;2(8):e474–e484.
78. Furlow B. COVACTA trial raises questions about tocilizumab's benefit in COVID-19. Lancet Rheumatol. cited 2020 Sep 15 2020;2(10): e592. Available from
79. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med. 2020;383 (24):2333–2344.
80. Caporali R, Favalli EG. Managing patients with rheumatic conditions during the COVID-19 pandemic. BMJ. 2020;369:m1633.
81. Zhang Y, Wang J, Zhao L, et al. Online management of rheumatoid arthritis during COVID-19 pandemic. Ann Rheum Dis. 2021;80(1): e4–e4.
82. Costa L, Tasso M, Scotti N, et al. Telerheumatology in COVID-19 era: a study from a psoriatic arthritis cohort. Ann Rheum Dis. 2020. cited 2021 Feb 1. Available from https://ard.bmj.com/content/early/2020/06/11/annrheumdis-2020-217806
83. Cassione EB, Zanframundo G, Biglia A, et al. COVID-19 infection in a northern-Italian cohort of systemic lupus erythematosus assessed by telemedicine. Ann Rheum Dis. 2020;79(10):1382–1383.
84. Furer V, Rondaan C, Heijstek MW, et al., 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 79(1): 39–52. 2020.

•• **Latest EULAR recommendations for vaccination.**

85. Rondaan C, Furer V, Heijstek MW, et al., Efficacy, immunogenicity and safety of vaccination in adult patients with autoimmune inflammatory rheumatic diseases: a systematic literature review for the 2019 update of EULAR recommendations. RMD Open. 5 (2): e001035. 2019.

• **A systematic literature review investigating the efficacy, immunogenicity and safety of vaccination in rheumatic patients.**

86. Oren S, Mandelboim M, Braun-Moscovici Y, et al. Vaccination against influenza in patients with rheumatoid arthritis: the effect of rituximab on the humoral response. Ann Rheum Dis. 2008;67 (7):937–941.
87. Bingham CO, Looney RJ, Deodhar A, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. Arthritis Rheum. 2010;62(1):64–74.
88. ACR-information-vaccination-against-SARS-CoV-2.pdf [Internet]. [cited 2021 Jan 1]. Available from: https://www.rheumatology.org/Portals/0/Files/ACR-Information-Vaccination-Against-SARS-CoV-2.pdf.
89. EULAR | EULAR view-points on SARS-CoV-2 vaccination in patients with RMDs [Internet]. [cited 2021 Jan 1]. Available from: https://www.eular.org/eular_sars_cov_2_vaccination_rmd_patients.cfm.
90. Houot R, Levy R, Cartron G, et al. Could anti-CD20 therapy jeopardise the efficacy of a SARS-CoV-2 vaccine? Eur J Cancer. 2020;136:4–6.
91. Baker D, Roberts CAK, Pryce G, et al. COVID-19 vaccine-readiness for anti-CD20-depleting therapy in autoimmune diseases. Clin Exp Immunol. cited 2021 Feb 1. 2020;202:149–161. Available from. 2.
92. Yun H, Xie F, Delzell E, et al. Comparative risk of hospitalized infection associated with biologic agents in rheumatoid arthritis patients enrolled in medicare. Arthritis Rheum. 2016;68 (1):56–66.
93. Schulze-Koops H, Krueger K, Vallbracht I, et al. Increased risk for severe COVID-19 in patients with inflammatory rheumatic diseases treated with rituximab. Ann Rheum Dis. 2020 cited 2021 Feb 7; 218075. Available from: https://ard.bmj.com/content/early/2020/06/25/annrheumdis-2020-218075
94. Martínez-Sanz J, Muriel A, Ron R, et al. Effects of tocilizumab on mortality in hospitalized patients with COVID-19: a multicentre cohort study. Clin Microbiol Infect. 2020. cited 2021 Feb 5. Available from: https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(20)30573-5/abstract
95. Sciascia S, Aprà F, Baffa A, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. Clin Exp Rheumatol. 2020;38(3):529–532.
96. Tleyjeh IM, Kashour Z, Damlaj M, et al. Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis. Clin Microbiol Infect. 2020 [cited 2021 Feb 5]. Available from: https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(20)30690-X/abstract

• **An updated systematic review and met-analysis on the efficacy and safety of tocilizumab in COVID-19.**

97. Fiolet T, Guihur A, Rebeaud ME, et al. Effect of hydroxychloroquine with or without azithromycin on the mortality of coronavirus disease 2019 (COVID-19) patients: a systematic review and meta-analysis. Clin Microbiol Infect. 2021;27(1):19–27.
98. Nguyen LS, Dolladille C, Drici M-D, et al. Cardiovascular toxicities associated with hydroxychloroquine and azithromycin: an analysis of the World Health Organization pharmacovigilance database. Circulation. 2020;142(3):303–305.

99. Chatre C, Roubille F, Vernhet H, et al. Cardiac complications attributed to chloroquine and hydroxychloroquine: a systematic review of the literature. Drug Saf. 2018;41(10):919–931.
100. Tselios K, Deeb M, Gladman DD, et al. Antimalarial-induced cardiomyopathy: a systematic review of the literature. Lupus. 2018;27(4):591–599.
101. Lane JCE, Weaver J, Kostka K, et al., Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study. Lancet Rheumatol. 2(11): e698–e711. 2020.
• **A retrospective study assessing the risk of cardiovascular events and complications in patients with RA receiving HCQ.**
102. Pollán M, Pérez-Gómez B, Pastor-Barriuso R, et al. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. Lancet. 2020;396(10250):535–544.
103. Stringhini S, Wisniak A, Piumatti G, et al. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study. Lancet. 2020;396(10247):313–319.
104. Carrat F, Lamballerie XD, Rahib D, et al. Seroprevalence of SARS-CoV-2 among adults in three regions of France following the lockdown and associated risk factors: a multicohort study. medRxiv. 2020;2020 sep 16.20195693.
105. Indagine di sieroprevalenza sul SARS-CoV-2 [Internet]. 2020 [cited 2020 Sep 27]. Available from: https://www.istat.it/it/archivio/243340.
106. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383(27):2603–2615.
107. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384(5):403–416.
108. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397:99–111.
109. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med. 2021 Feb 24 NEJMoa2101765. 10.1056/NEJMoa2101765.
110. Park JK, Lee YJ, Shin K, et al. Impact of temporary methotrexate discontinuation for 2 weeks on immunogenicity of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomised clinical trial. Ann Rheum Dis. 2018;77(6):898–904.
111. Hua C, Barnetche T, Combe B, et al. Effect of methotrexate, anti–tumor necrosis factor α, and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: a systematic review and meta-analysis. Arthritis Care Res. 2014;66(7):1016–1026.