Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Therapies (2020) **75**, 335—342

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COVID-19

Challenges of autoimmune rheumatic disease treatment during the COVID-19 pandemic: A review

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Received 25 June 2020; accepted 25 June 2020
Available online 27 June 2020

KEYWORDS
Pharmacology;
Rheumatology;
Rheumatoid arthritis;
Dexamethasone;
Hydroxychloroquine

Summary Since December 2019, the COVID-19 pandemic has become a major public health problem. To date, there is no evidence of a higher incidence of COVID in patients with autoimmune rheumatic diseases and we support the approach of maintaining chronic rheumatological treatments. However, once infected there is a small but significant increased risk of mortality. Among the different treatments, NSAIDs are associated with higher rates of complications, but data for other drugs are conflicting or incomplete. The use of certain drugs for autoimmune inflammatory rheumatisms appears to be a potentially interesting options for the treatment. The rationale for their use is based on the immune system runaway and the secretion of pro-inflammatory cytokines (Il1, IL6, TNFα) in severe forms of the disease. Notably, patients on chloroquine or hydroxychloroquine as a treatment for their autoimmune rheumatic disease are not protected from COVID-19.

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https://doi.org/10.1016/j.therap.2020.06.013

Abbreviations

ANCA	anti-neutrophil cytoplasmic antibodies
ARDS	acute respiratory distress syndrome
bDMARDS	biological disease-modifying antirheumatic drugs
COVID-19	novel coronavirus disease 2019
csDMARDS	conventional synthetic disease modifying antirheumatic drugs
HCQ	hydroxychloroquine
ICU	intensive care unit
IL1	interleukin 1
IL6	interleukin 6
JAK	janus kinase (inhibitors)
MERS-COV	middle East respiratory syndrome coronavirus
NSAIDs	non-steroidal anti-inflammatory drugs
RA	rheumatoid arthritis
RNA	ribonucleic acid
SARS-COV2	severe acute respiratory syndrome coronavirus 2
SLE	systemic lupus erythematosus
SSc	systemic sclerosis
tsDMARDS	targeted synthetic disease modifying antirheumatic drugs
TCZ	tocilizumab
TNF	tumor necrosis factor
WHO	World Health Organization

Introduction

In December 2019, a new respiratory infection caused by a member of the coronoviridae family called severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) was reported in Wuhan, China [1]. The infection spread rapidly and became a worldwide pandemic. The virus-related illness, called novel coronavirus disease 2019 (COVID-19), is characterized by a respiratory picture (cough, fever, dyspnea and fatigue) accompanied by lymphopenia [2]. In the most severe cases, the disease causes interstitial lung disease with severe alveolar damage that can lead to acute respiratory distress and death [3—5]. Cases are still in constant evolution with 8,006,427 confirmed cases of COVID-19, including 436,899 deaths, reported to the World Health Organization (WHO) as of 17 June 2020 [6]. In this pandemic context, it is important to clarify the link between COVID-19 and the potentially most fragile patients, and we focus here on those suffering from autoimmune diseases.

Autoimmune rheumatic diseases are a heterogeneous group of diseases linked to significant activation of the immune system. The most common of these pathologies are rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ankylosing spondylitis, psoriatic rheumatism, scleroderma and systemic vasculitides [7]. These patients are particularly at risk of complications of pulmonary infection. This may be related to their index disease itself, as some of these diseases (e.g. rheumatoid arthritis, scleroderma, systemic lupus erythematosus) are often associated with interstitial lung disease or other pulmonary diseases [8—10], or to their immunosuppressive treatments such as corticosteroids and synthetic or biological disease-modifying drugs. In addition, cardiovascular co-morbidities related to diseases such as rheumatoid arthritis may increase the risk of morbidity, as cardiovascular diseases have also been identified as a risk factors for COVID-related morbidity and mortality [11,12].

The increasing understanding of the COVID-19 has led to a growing interest in certain drugs used in these pathologies, including some non-specific antivirals and immunomodulators [13]. Chloroquine or hydroxychloroquine, particularly used in SLE, have been tested in many research protocols focusing on treatment of the infection or in postexposure prophylaxis [14—17]. The rational for use of other antirheumatic drugs is based on the inflammatory reaction associated with the cytokine storm (i.e. hyperproduction of interleukin 1 [IL1], interleukin 6 [IL6], tumor necrosis factor [TNF] α, etc.) in advanced forms of COVID-19 [18—21].

For these reasons, the relationship between COVID-19 infection and the management of patients with autoimmune rheumatic disease is complex. The objective of this review is to provide a short overview of the risk of COVID-19 infection-related to these diseases and to focus on the treatments used.

Are patients with autoimmune rheumatic disease a population at risk of severe COVID-19?

Since the beginning of the pandemic, concerns have been expressed about the risk of SARS-CoV-2 infection and its complications in patients with systemic autoimmune diseases [22]. The relationship between autoimmune disease and COVID-19 infection is quite complex and can be interpreted in different ways.

First, several studies have shown that patients with autoimmune rheumatic diseases are at greater risk of infectious complications than the general population [23]. In rheumatoid arthritis, a history of smoking, corticosteroid use and rheumatoid factor were found to be significantly independent predictors of infection-related hospitalization [24].

During the COVID-19 pandemic, the question of excess mortality linked to autoimmune diseases soon arose. In many initial reports, autoimmune diseases were not reported as a risk factor for morbidity. However, most of these initial observational studies were incomplete in terms of patient phenotyping. Co-morbidities such as hypertension, coronary heart disease and diabetes were associated with a significantly higher risk of death amongst COVID-19 patients [25]. However, these same co-morbidities are associated with autoimmune rheumatic diseases [26—29]. A key British study reported health data collected between February and 25 April 2020 on 17.5 million Britons with 5683 hospital deaths due to COVID-19. Among the identified risk factors for mortality were autoimmune rheumatic diseases with an adjusted hazard ratio of 1.23 (95% confidence interval [95% CI] 1.12—1.35). However, although emerging as a potential risk factor, it remains very moderate compared to other factors, including advanced age, being male, morbid obesity, hematological malignancy, organ transplant and uncontrolled diabetes [30]. The data from the French cohort

should help us to define whether this excess risk is common to the various autoimmune rheumatic diseases.

Another issue is whether patients with autoimmune rheumatic diseases are at increased risk of COVID-19 incidence compared to the general population, given that immunosuppressive treatments, such as corticosteroids and other immune-modulators increase this risk [31,32]. In an observational study in Tuscany (Italy), SARS-CoV-2 infection was evaluated among 458 patients with systemic autoimmune diseases [33]. Only one case of confirmed SARS-CoV-2 infection was found, resulting in a prevalence of SARS-CoV-2 infection similar to that observed in the general population, suggesting that patients with systemic autoimmune diseases do not carry an increased risk of SARS-CoV-2 infection. Another study in Italy looked at the impact of COVID-19 in patients with connective tissue disorders [34]. The overall study population included 123 adult patients (110 females) with SLE ($n = 61$), systemic sclerosis (SSc; $n = 43$), undifferentiated connective tissue disease ($n = 9$), or Sjögren's syndrome ($n = 10$). About 60% of patients were treated with conventional synthetic disease-modifying drugs, 20% were on biological agents and 64.2% were also taking corticosteroids (mean dose 5.3 mg daily). The only recorded patient with a SARS-CoV-2 positive swab was a 32-year-old woman with SSc and pulmonary involvement treated with hydroxychloroquine and rituximab. She developed a severe pattern of COVID-19 with interstitial pneumonia requiring hospitalization in intensive care unit, where she died, despite intubation and an attempt with tocilizumab. In the same period of observation, the incidence of COVID-19 positivity in their region was consistent with that they observed in their cohort (0.62% vs. 0.81%, respectively). Monti et al. studied the clinical course of COVID-19 in a series of patients with chronic arthritis treated with targeted immunosuppressive therapies [35]. The authors collected information on 320 patients (68% female, mean age 55 ± 14 years) treated with biological disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic disease modifying antirheumatic drugs (tsDMARDs): 57% with rheumatoid arthritis, 43% with spondyloarthritis, 52% treated with tumor necrosis factor inhibitors, 40% with other bDMARDs and 8% with tsDMARDs. Thirteen confirmed and/or suspected COVID-19 patients were diagnosed (only 4 confirmed). None of the patients with a confirmed diagnosis of COVID-19 or with a highly suggestive clinical picture developed severe respiratory complications or died. Only one patient, aged 65, required admission to hospital and low-flow oxygen supplementation for a few days.

Another large Italian study was conducted between 20 February and 7 April 2020 [36]. The authors collected clinical data on 859 patients affected by different autoimmune rheumatic diseases and sarcoidosis, treated with a stable full dosage of bDMARDs or tsDMARDs. Only two patients were diagnosed with COVID-19. The first patient was a 50-year-old woman affected by rheumatoid arthritis and treated with rituximab since 2016. She presented bilateral diffuse pneumonia. She was hospitalized and discharged 2 days later after lopinavir-ritonavir treatment. The other patient was an 87-year-old woman with diabetes mellitus and treatment with tocilizumab for 9 months for giant cell arteritis. She underwent a nasal-pharyngeal swab with a positive result as part of screening at the retirement home with confirmed symptomatic cases of COVID-19. She remained asymptomatic without interrupting biological therapy. Overall, these results do not support a higher incidence of SARS-CoV-2 infection in this population and supports the approach of maintaining chronic rheumatological treatments [37] and adherence to infection control measures, thus avoiding a relapse of rheumatic disease without increasing the risk of COVID-19.

What is the impact of treatments for autoimmune rheumatic diseases on COVID-19?

NSAIDs

Outside of the current pandemic, a recent review of case-controlled studies suggests that non-steroidal anti-inflammatory drugs (NSAIDs) are associated with higher rates of complications after respiratory tract infections, including complicated pneumonia, suppuration, etc. [38].

Gianfrancesco et al. reported data from the COVID-19 Global Rheumatology Alliance registry where a total of 600 cases with rheumatic disease were included from 40 countries [39]. NSAID use was reported less frequently among hospitalized patients than non-hospitalized patients (16% vs. 25%, $P = 0.02$), while there was a higher proportion of patients receiving high doses of glucocorticoids among those who were hospitalized than not hospitalized (16% vs. 7% for doses = 10 mg/day, $P = 0.01$).

While the existing literature does not currently provide conclusive evidence for or against the use of NSAIDs in the treatment of COVID-19 patients [40,41], reasonable evidence exists of a link between NSAIDs and respiratory adverse effects in several settings, and we advocate against the use of NSAIDs during the COVID [42].

Corticosteroids

Dexamethasone significantly reduces the duration of mechanical ventilation and mortality in patients with moderate to severe acute respiratory distress syndrome (ARDS) admitted to intensive care units [43]. As such, outside of the COVID-19 pandemic period, dexamethasone is sometimes used in acute respiratory distress syndromes in intensive care. However, the use of corticosteroids during the COVID-19 pandemic remains controversial [44].

A meta-analysis of the impact of corticosteroid therapy on outcomes of persons infected with SARS-CoV-2, SARS-CoV and middle East respiratory syndrome coronavirus (MERS-CoV), was conducted and included 10 observational studies and one randomized clinical trial. Notably, 6 of the 11 studies concerned SARS-CoV and MERS-CoV infections. This meta-analysis draws the conclusion that corticosteroids neither reduced the risk of death, nor reduced hospitalization duration or intensive care unit (ICU) admission, and had adverse effects [45]. In addition, Wang et al. reported that 44.9% of their 138 patients admitted for COVID-19 received corticosteroid therapy with no effect on morbidity and mortality [46]. However, the likelihood of selection bias is

extremely high in these observational studies, since corticosteroids are more likely to be given for severe infections.

Conversely, methylprednisolone (1—2 mg/kg per day) use was reported in 19% of the early Chinese COVID-19 patients [5], recommended and suggested to be beneficial and without either delaying SARS-CoV-2 ribonucleic acid (RNA) clearance or influence IgG antibody production [47].

Among patients with autoimmune rheumatic diseases, in the COVID-19 Global Rheumatology Alliance registry, glucocorticoid therapy at prednisone-equivalent doses $\geq$ 10 mg/day, was associated with a higher odds of hospitalization compared with no glucocorticoid therapy in and adjusted analysis (OR = 2.05, 95% CI 1.06 to 3.96; $P = 0.03$) [39].

The final answer will come from randomized controlled trials. The RECOVERY study enrolled 2104 patients randomized to receive dexamethasone (6 mg once daily either orally or by intravenous injection) for ten days compared to 4321 patients receiving usual care. A preprint article published on 22 June 2020 indicates that dexamethasone reduces deaths by a third in ventilated patients and by a fifth in other patients receiving only oxygen [48]. The result of other randomized studies are pending [49] (NCT04244591). Until the full publication of the RECOVERY study, the WHO guidelines not support routinely giving systemic corticosteroids for treatment of viral pneumonia [50], but this is likely to change in the near future.

Conventional synthetic disease modifying antirheumatic drug (csDMARDs). CsDMARDS are widely used for autoimmune rheumatic diseases

Methotrexate is indicated in particular in rheumatoid arthritis (RA) and psoriasic rheumatis. Much data is available for this drug, independently from COVID-19. Compared to placebo, it has been associated with a small but significant increased risk of infection in RA (RR: 1.25; 95% CI, 1.01—1.56; $P = 0.04$; $I^2 = 0\%$), but not in other non-RA inflammatory rheumatic diseases populations [51]. Another meta-analysis conducted in RA patients confirmed a small increased risk of all adverse respiratory events (RR 1.10, 95% CI 1.02—1.19) and respiratory infections (RR 1.11, 95% CI 1.02—1.21). In addition, methotrexate was shown to increase herpes zoster viral infections [52,53]. However, no studies have shown an increased risk of COVID-19 infection for patients on methotrexate.

bDMARDs (biological disease modifying antirheumatic drugs)

Several studies have shown that bDMARDs compared with patients on conventional sDMARDs had a higher risk of serious infection [54].

AntiTNFα

During respiratory distress syndromes, pro-inflammatory cytokines such as TNFα are secreted. Therefore, it has been postulated that the use of TNF inhibitors may be effective in reducing both SARS-CoV2 infection and the consequent organ damage [55]. A study evaluating adalimumab in COVID-19, especially in severe infections has recently been registered in the Chinese Clinical Trial Registry (ChiCTR2000030089).

Tocilizumab

Tocilizumab (TCZ) is a recombinant human IL6 monoclonal antibody, which specifically binds to soluble and membrane-bound IL6 receptors (IL6R), thus blocking IL6 signaling and the inflammatory response it mediates. TCZ is widely used in rheumatic diseases, such as RA.

Several retrospective studies have shown the potential efficacy of TCZ in severe forms of COVID-19 [56]. For example, in a report from China by Xu et al. the authors were able to show that tocilizumab effectively improved clinical symptoms in COVID-19 patients. Within 5 days after tocilizumab administration, 15 of the 20 patients had lowered their oxygen intake and 19 of the 20 showed a noticeable improvement on their lung CT scan [57]. Currently, several randomized interventional studies are underway to determine the efficacy of IL6 inhibitor therapies (NCT04370834, NCT04330638, NCT04345445 and NCT04331808).

JAK inhibitors

Janus kinase (JAK) inhibitors have indications in both in RA and psoriatic arthritis. Incidence rates of herpes zoster infection reported for tofacitinib and baracitinib were higher than those usually observed in patients with RA [58,59]. However, risks for COVID-19 patients with COVID-19 on these therapies have not been demonstrated.

Moreover, in relation to their mechanism of action, the potential use of JAK inhibitors and in particular baracitinib is currently being explored in severe COVID-19 patients. Firstly, Richardson et al. suggested the use of baricitinib for the drug treatment of COVID-19 cases requiring hospitalization [60]. Indeed, this drug inhibits enzyme kinases attenuating the infectivity of the virus (by preventing it from entering the cells via inhibition of clathrin-mediated endocytosis) and could prevent excessive inflammation.

In a single arm study of 12 patients with moderate COVID-19 pneumonia treated with baricitinib and lopinavir/ritonavir [61], compared with a cohort previously treated with ''standard of care'' (lopinavir/ritonavir and hydroxychloroquine), the group administered baricitinib had fewer ICU transfers (0% vs. 33%) and a higher discharge rate at week 2 (58% vs. 8%).

However, evidence for the use of baricitinib to treat COVID-19 remains extremely scarce. Furthermore, data are not sufficient to continue JAK inhibitors in all patients taking these medications who develop SARS-CoV-2 infection [62]. Further clinical trials and detailed analysis are warranted to confirm efficacy of Jak inhibitors in severe forms (NCT04393051, ChiCTR2000030170, ChiCTR2000029580).

Rituximab

Several cases of COVID-19 have been reported in patients who had received rituximab for lymphoma [63], multiple sclerosis [64], and also autoimmune rheumatic diseases such as scleroderma [65] and anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis [66]. Some of these observations seem to exhibit a prolonged course with

delayed worsening. This corresponds to an unusual presentation of COVID-19 and suggests an impact of rituximab in immune response against SARS-COv-2. Independently from COVID-19, rituximab may induce (sometimes life-threatening) infections mainly in the 2—3 months following its administration [67]. Several mechanisms have been advanced, which could also contribute to the unusual presentation in COVID-19: impaired B cell and humoral responses, impaired antigen presentation and cooperation with other immune-competent cells [68]. In addition, rituximab could decrease the immunological memory against SARS-Cov-2, which is a crucial point because of the long-lasting effects of this drug on B cells. Whatever, further data are needed to precise the characteristics of COVID-19 in rituximab-treated patients.

Is there a prophylactic effect of hydroxychloroquine on COVID-19 in patients with autoimmune rheumatic diseases?

Chloroquine and hydroxychloroquine are widely used anti-malarial drugs with well-known immunomodulatory properties whose use has been extended to several autoimmune rheumatic diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).

Both chloroquine and hydroxychloroquine (HCQ) have immunomodulatory effects. In general, HCQ has fewer and less severe toxicities and fewer drug interactions than chloroquine. The proposed mechanisms of action and rationale for use of both drugs for COVID-19 is the increase in the endosomal pH, inhibiting toll-like receptor activity, and interfering with terminal glycosylation of the cellular receptor ACE 2 and the host cell membranes. All these functions may negatively influence virus-receptor binding, resulting in a potential effect of the drug on SARS-CoV cell entry. In vitro, both chloroquine and HCQ may block the transport of SARS-CoV-2 from early endosomes to endolysosomes, in view of the in vitro activity of chloroquine against SARS-CoV [69,70]. Despite the potential efficacy of hydroxychloroquine in vitro, to date, no evidence supports its use as a COVID-19 treatment [17]. However, the question remains regarding patients already using this treatment before being exposed to SARS-CoV-2.

Several descriptive studies in patients with autoimmune rheumatic diseases do not support a protective action of chronic hydroxychloroquine use in this population. In France, the clinical course of 17 patients with COVID-19 and SLE treated long-term with hydroxychloroquine, with a median duration of treatment of 7.5 years was described. All patients had hydroxychloroquine blood concentrations within the therapeutic range. In these patients, long-term hydroxychloroquine therapy did not appear to be protective, including for two with fatal outcomes [71]. In addition, the more recent published data from the ''COVID-19 Global Rheumatology Alliance'' registry shows that out of 600 patients with chronic autoimmune rheumatic diseases and COVID-19 infection, taking anti-malarial drugs such as hydroxychloroquine does not reduce the hospitalization rate [39]. In another cohort of 120 patients with SLE, the percentage of patients with symptoms of COVID-19 did not differ between those taking HCQ (6.9%) and those who were not (6.3%) [72]. In the United States (Michigan), a rheumatology clinic diagnosed 31 cases of COVID-19. Of these, five patients (16%) had SLE of which four were taking hydroxychloroquine. Of the lupus patients, five were hospitalized, three required ventilation, and one died as a result of the infection. These rates were higher than expected, suggesting that lupus patients treated long-term with hydroxychloroquine are prone to develop more severe forms of COVID-19 compared to patients with other autoimmune diseases [73].

Moreover, the majority of lupus patients treated long-term with HCQ achieved plasma drug concentrations that were lower than those proven to be effective in vitro against SARS-CoV2 [74]. Thus, a preventive role of hydroxychloroquine, when administered chronically in lupus or rheumatoid arthritis is unlikely.

Conclusion

Patients with autoimmune rheumatic diseases are at increased risk of infections and cardiovascular co-morbidities. Nevertheless, they do not clearly appear to be at increased risk of COVID-19, but rather have a small increased risk of developing severe forms. Hydroxychloroquine in autoimmune rheumatic diseases exhibits no clinical prophylactic efficacy for COVID-19. Other therapies, which may act on the exacerbated auto-inflammatory response and cytokine storm in the later stages of the infection (anti-IL6, AntiTNFα) are currently being tested.

Disclosure of interest

The authors declare that they have no competing interest.

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